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Two-way Interaction Effects of Perioperative Complications on 30-Day Mortality in General Surgery

Minjae Kim[1,2] · **Guohua Li**[1,2]

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Abstract

Background Multiple perioperative complications increase mortality risk, and certain complications synergistically increase this risk to a greater degree than might be expected if the complications were independent, but these effects are not well established.

Methods This is a retrospective cohort study of 422,827 intraabdominal general surgery patients (American College of Surgeons National Surgical Quality Improvement Program 2005–2011). Eight complications were evaluated: acute respiratory failure (ARF), acute kidney injury (AKI), sepsis/septic shock, stroke, cardiac arrest (CA), myocardial infarction (MI), deep vein thrombosis/pulmonary embolus, and transfusion. Each combination of two complications (28 total) was modeled using a Cox model for 30-day mortality, with adjustment for preoperative comorbidities and risk factors. Additive interaction was determined with the relative excess risk due to interaction (RERI). A positive RERI indicates that the mortality risk with both complications is greater than the sum of the individual mortality risks. Bonferroni correction was applied ($\alpha = 0.05/28 = 0.0018$).

Results Seven combinations demonstrated positive interaction: sepsis-CA (RERI 88.1; $p < 0.0001$), ARF–AKI (RERI 50.5; $p < 0.0001$), AKI–sepsis (RERI 33.9; $p < 0.0001$), sepsis–stroke (RERI 33.9; $p < 0.0001$), ARF–stroke (RERI 32.3; $p < 0.0001$), AKI–MI (RERI 24.5; $p = 0.0013$), and ARF–sepsis (RERI 19.2; $p < 0.0001$). Two combinations demonstrated negative interaction: ARF–CA (RERI −65.1; $p = 0.0017$) and CA-transfusion (RERI −52.0, $p < 0.0001$).

Conclusions Interaction effects exist between certain complications to increase the risk of short-term mortality. ARF, AKI, sepsis, and stroke were most likely to be involved in positive interactions. Further research into the mechanisms for these effects will be necessary to develop strategies to minimize the compounding effects of multiple complications in the perioperative period.

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✉ Minjae Kim
mk2767@cumc.columbia.edu

Guohua Li
gl2240@cumc.columbia.edu

[1] Department of Anesthesiology, Columbia University Medical Center, 622 West 168th Street, PH 5 Suite 505C, New York, NY 10032, USA

[2] Department of Epidemiology, Columbia University Mailman School of Public Health, New York, NY, USA

Introduction

Perioperative complications lead to morbidity and suboptimal hospital outcomes in critically ill surgical patients, with longer hospital stays and higher readmission rates, costs, and mortality [1–4]. The causes of complications are multifactorial, and each can increase the risk of developing others. While it is not surprising that multiple complications increase mortality risk [5], the specific relationships between complications have not been fully investigated. In particular, certain complications may increase the risk of postoperative mortality to a greater degree than might be expected by the independent effects of each complication alone. Indeed, we demonstrated that significant additive interaction effects exist between acute kidney injury (AKI), acute respiratory failure (ARF), and sepsis/septic shock in high-risk general surgery patients [6]. Specifically, any two of these complications synergistically increased postoperative mortality risk, making it imperative to closely monitor patients with a complication to ensure that another does not develop.

It is unknown whether any other major complications have synergistic effects with regard to postoperative mortality. Using a cohort of intraabdominal general surgery patients from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP), we evaluated interaction effects among eleven major perioperative complications to identify the specific complications that merit further investigation regarding synergistic effects on postoperative mortality. This knowledge will help to identify the biological and clinical pathways underlying these effects so that measures to reduce the incidence of these complications and postoperative mortality can be identified.

Methods

Data

This study was not subject to local IRB review as it did not require access to protected health information. The ACS-NSQIP[1] is a validated, prospectively collected national dataset aimed at improving surgical quality and outcomes [7]. Data include demographic characteristics, presurgical comorbidities, intraoperative variables, and 30-day postoperative morbidity and mortality data. The systematic sampling process and criteria for maintaining the high quality of the dataset have been described [8].

Patient selection

Intraabdominal general surgery patients from the 2005–2011 ACS-NSQIP were identified. The Clinical Classifications Software for Services and Procedures (Agency for Healthcare Research and Quality, Rockville, MD)[2] classified procedures based on the primary Current Procedural Terminology code. Fourteen categories were identified (Supplemental Table 1), resulting in an initial sample of 795,154 records. *Outpatients* were excluded ($N = 209{,}936$) as they have a low risk of adverse perioperative outcomes. Those with the following preoperative acute complications were excluded: (1) acute renal failure/dialysis ($N = 10{,}627$), (2) mechanical ventilation ($N = 9119$), (3) pneumonia (4466), (4) sepsis ($N = 91{,}787$), (5) wound infection ($N = 19{,}820$), (6) transfusions ($N = 6897$), or had missing data on these variables ($N = 61{,}642$). The final sample consisted of 422,827 records.

Baseline demographic and operative variables

Patients who are 90 years old or older were reported as being 90 years old. Race/ethnicity was categorized as white versus non-white. Body mass index (BMI) was calculated from height and weight data. The estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula incorporating creatinine, sex, age, and race [9] and categorized into groups corresponding to the stages of chronic kidney disease (CKD) [10]: *<30*, *30–60*, *60–90*, *>90,* or *missing*. Not all patients require a full laboratory workup prior to surgery, and a missing value may be an important prognostic indicator for perioperative morbidity and mortality. Data on cancer history and perioperative blood transfusions were collected as described previously [6].

Clinical end points

We evaluated eleven major perioperative outcomes: (1) AKI, (2) ARF, (3) cardiac arrest, (4) deep vein thrombosis/pulmonary embolus (DVT/PE), (5) myocardial infarction (MI), (6) organ space infection, (7) pneumonia, (8) sepsis/septic shock, (9) stroke, (10) transfusion, and (11) wound dehiscence. Several outcomes are composites of two separate ACS-NSQIP outcomes (Supplemental Table 2). The

[1] The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in the ACS-NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

[2] http://www.hcup-us.ahrq.gov/toolssoftware/ccs_svcsproc/ccssvcproc.jsp, Accessed 6/15/12.

dataset identifies the postoperative day in which each complication, including mortality, occurred.

Statistical analysis

The differences in preoperative patient characteristics and comorbidities between those without complications and those developing at least one complication were compared with a *t* test for continuous variables and the chi-squared test for categorical variables. Cox proportional hazard modeling [11] was used to calculate hazard ratios (HRs) for 30-day mortality, with perioperative complications modeled as time-dependent variables to account for the postoperative day in which they occurred [12]. Based on prior analyses, age, BMI, hematocrit, and log(operative time) were entered as continuous variables [6]. For multivariable analyses, we separately evaluated each potential adjustment variable in a Cox model including all eleven complications. Variables with $P < 0.0001$ were initially considered, and only those with $P < 0.01$ in the multivariable model were retained. After determining the final adjustment variables, we retained complications with $P < 0.01$ in the fully adjusted model. The population attributable fraction was calculated as previously described [13] using the formula: $pd\left(\frac{HR-1}{HR}\right)$ where *pd* is the proportion of cases with the given complication and *HR* is the adjusted hazard ratio for mortality for the complication. Confidence intervals for the population attributable fractions were determined using 1000 bootstrapped samples with appropriate corrections for bias as described [14].

Each combination of two complications was assessed for additive interaction using the relative excess risk due to interaction (RERI) [15] in separate adjusted Cox models. The RERI determines whether there is additive interaction in models that are inherently multiplicative [16], with additive interaction being the empirical method to determine biological interaction [17]. Bonferroni correction accounted for multiple comparisons [18]. Statistical analyses were performed using SAS Software version 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics of patients

The final sample included 422,827 intraabdominal general surgery patients, and 51,390 (12%) developed at least one perioperative complication (Table 1). Those with complications were more likely older, male, with preoperative risk factors, including cardiovascular disease, pulmonary disease, chronic kidney disease, functional dependence, and cancer. Interestingly, those with complications were less likely to be undergoing an emergent procedure.

Perioperative complications and 30-day mortality

The most common complications were transfusion (5.3%), sepsis/septic shock (3.9%), organ space infection (2.5%), and ARF (2.1%) (Table 2). Overall, 1.1% of patients died within 30 days of surgery, but among those developing at least one complication, the mortality was 6.6%. Cardiac arrest (74%), AKI (23%), ARF (23%), and stroke (20%) were associated with the greatest mortality.

All complications were significantly associated with 30-day mortality in individual univariable models (Table 3, first column), with HRs [95% CI] ranging from 6.94 [6.49, 7.42] with perioperative transfusions to 388 [362, 417] with cardiac arrest. After adjusting for risk factors, each complication remained significantly associated with 30-day mortality, with HRs [95% CI] ranging from 2.19 [2.02, 2.37] with perioperative transfusions to 135 [125, 146] with cardiac arrest (Table 3, second column).

Cox models incorporating all of the complications into a single model were fit to the data. An initial model including all eleven perioperative complications, adjusted for risk factors, found that three complications were not associated with mortality: pneumonia (HR 1.01, $P = 0.80$), wound dehiscence (HR 1.20, $P = 0.06$), and organ space infection (HR 0.98, $P = 0.78$). These complications were removed from further consideration. The model including the remaining 8 complications, adjusted for risk factors, demonstrated that all of the remaining complications were significantly associated with mortality with HRs [95% CI] ranging from 1.26 [1.11, 1.43] (DVT/PE) to 21.0 [19.2, 23.1] (cardiac arrest) (Table 4).

The population attributable fraction was calculated for each complication to estimate the percentage of mortality in the population that might be eliminated if the complication was prevented [13]. The population attributable fractions ranged from 0.11% [95% CI; 0.04%, 0.16%] with MIs to 2.8% [2.6%, 2.9%] with sepsis/septic shock (Table 4).

Patients developing multiple complications

A total of 43,486 patients developed at least one of the 8 perioperative complications that were significant in multivariable analyses. Of these, 75% ($N = 32,517$) had only one complication (Fig. 1a), while 25% ($N = 10,969$) developed multiple complications. Postoperative mortality was an increasing function of the number of complications that developed (Fig. 1b). While those not developing a complication had a mortality of

Table 1 Characteristics of patients undergoing intraabdominal general surgery by perioperative morbidity status, American College of Surgeons National Surgical Quality Improvement Program, 2005–2011

	No Complication		Complication[a]		*P*-value
	371,437		51,390		
Age (years)	53.1	(17.1)	62.2	(15.7)	*
Female	224,297	(60.5)	26,536	(51.7)	*
White	262,134	(70.6)	37,412	(72.8)	*
ASA physical status					*
1	29,418	(7.9)	825	(1.6)	
2	177,382	(47.8)	14,782	(28.8)	
3	154,558	(41.7)	30,793	(60.0)	
4	9556	(2.6)	4851	(9.5)	
5	74	(0.0)	95	(0.2)	
Body mass index (kg/m^2)	32.2	(13.1)	29.2	(8.7)	*
Emergency	61,008	(16.4)	6874	(13.4)	*
Diabetic	55,384	(14.9)	10,368	(20.2)	*
Dyspnea	38,792	(10.4)	7503	(14.6)	*
Chronic obstructive pulmonary disease	12,159	(3.3)	3968	(7.7)	*
Current smoker	66,878	(18.0)	10,144	(19.7)	*
Congestive heart failure	1286	(0.4)	643	(1.3)	*
Myocardial infarction	867	(0.2)	435	(0.9)	*
Coronary revascularization (PCI or CABG)	24,293	(6.5)	6473	(12.6)	*
Angina	1508	(0.4)	465	(0.9)	*
Hypertension	159,633	(43.0)	28,681	(55.8)	*
Peripheral vascular disease	2977	(0.8)	1060	(2.1)	*
Stroke (with or without neurological deficit)	13,752	(3.7)	3891	(7.6)	*
Functionally dependent	10,160	(2.7)	4730	(9.2)	*
Ascites	3255	(0.9)	1436	(2.8)	*
Varices	434	(0.1)	240	(0.5)	*
Hematocrit					*
Low $\leq$ 34	48,107	(13.0)	17,800	(34.6)	
Medium 34–44	250,543	(67.5)	27,124	(52.8)	
High $>$ 44	49,057	(13.2)	4496	(8.8)	
Hct missing	23,730	(6.4)	1970	(3.8)	
Steroid use	11,558	(3.1)	3278	(6.4)	*
Cancer	79,404	(21.4)	24,573	(47.9)	*
Bleeding disorder	12,409	(3.3)	3938	(7.7)	*
Hematocrit (%)	39.2	(4.8)	36.3	(6.0)	*
Estimated glomerular filtration rate (mL/min/1.73 m^2)					*
$<$30	3758	(1.0)	1557	(3.0)	
30–60	39,120	(10.5)	9770	(19.0)	
60–90	127,129	(34.2)	19,199	(37.4)	
$>$90	166,559	(44.8)	18,261	(35.5)	
Missing	34,871	(9.4)	2603	(5.1)	

Continuous variables expressed as mean (SD). Categorical variables expressed as counts (%)

ASA American Society of Anesthesiologists, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft

* $P < 0.0001$

[a] Complications include: acute kidney injury, acute respiratory failure, cardiac arrest, deep vein thrombosis/pulmonary embolus, myocardial infarction, organ space infection, pneumonia, sepsis/septic shock, stroke, transfusion, and wound dehiscence

Table 2 Perioperative complications in patients undergoing intraabdominal general surgery, American College of Surgeons National Surgical Quality Improvement Program, 2005–2011

	Complication		Mortality among complication	
	N	%	*N*	%
Total sample	422,827		4438	1.1
Composite morbidity	51,390	12	3367	6.6
Transfusion	22,455	5.3	1204	5.4
Sepsis/septic shock	16,411	3.9	1720	10
Organ space infection	10,469	2.5	357	3.4
Acute respiratory failure	8916	2.1	2007	23
Pneumonia	7137	1.7	857	12
DVT/PE	4943	1.2	279	5.6
wound dehiscence	3363	0.8	131	3.9
Acute kidney injury	3308	0.8	754	23
Cardiac arrest	1352	0.3	1000	74
Myocardial infarction	1212	0.3	234	19
Stroke	669	0.2	133	20

DVT deep vein thrombosis, *PE* pulmonary embolus

Table 3 Cox models for 30-day mortality in patients undergoing intraabdominal general surgery, American College of Surgeons National Surgical Quality Improvement Program, 2005–2011

	Complication only			Complication and risk factors[a]		
Complication	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Cardiac arrest	388	[362, 417]	*	135	[125, 146]	*
Acute respiratory failure	58.0	[54.6, 61.5]	*	21.8	[20.3, 23.3]	*
Acute kidney injury	50.3	[46.5, 54.5]	*	20.0	[18.3, 21.9]	*
Stroke	33.7	[28.3, 40.0]	*	9.52	[7.96, 11.4]	*
Sepsis/septic shock	28.7	[27.0, 30.6]	*	12.8	[11.9, 13.7]	*
Myocardial infarction	27.8	[24.4, 31.7]	*	7.43	[6.47, 8.54]	*
Pneumonia	21.1	[19.5, 22.7]	*	7.04	[6.49, 7.64]	*
Deep vein thrombosis/pulmonary embolus	10.3	[9.12, 11.6]	*	3.79	[3.34, 4.31]	*
Wound dehiscence	7.13	[5.99, 8.49]	*	3.11	[2.59, 3.73]	*
Organ space infection	7.05	[6.31, 7.87]	*	4.39	[3.91, 4.92]	*
Transfusion	6.94	[6.49, 7.42]	*	2.19	[2.02, 2.37]	*

Each Cox model includes only one perioperative complication variable (i.e., separate Cox model for each complication). The complication variable was modeled as a time-dependent covariate

HR hazard ratio, *CI* confidence interval

* $P < 0.0001$

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

Table 4 Cox model for 30-day mortality in patients undergoing intraabdominal general surgery, adjusted for preoperative comorbidities and risk factors, American College of Surgeons National Surgical Quality Improvement Program, 2005–2011

Complication	HR	95% CI	*P*-value	PAF (%)	95% CI[a]
Cardiac arrest	21.0	[19.2, 23.1]	*	0.30	[0.29, 0.32]
Acute respiratory failure	4.84	[4.40, 5.32]	*	1.7	[1.6, 1.7]
Stroke	4.12	[3.44, 4.94]	*	0.12	[0.10, 0.13]
Sepsis/septic shock	3.60	[3.31, 3.92]	*	2.8	[2.6, 2.9]
Acute kidney injury	2.96	[2.69, 3.26]	*	0.52	[0.46, 0.57]
Myocardial infarction	1.59	[1.38, 1.84]	*	0.11	[0.04, 0.16]
Transfusion	1.34	[1.24, 1.46]	*	1.4	[0.74, 1.9]
Deep vein thrombosis/pulmonary embolus	1.26	[1.11, 1.43]	0.0006	0.24	[0.00, 0.46]

The Cox model includes all relevant perioperative complication variables (i.e., single Cox model for complications). The complication variables are modeled as time-dependent covariates

Adjustment variables include: age, female sex, white race, body mass index, emergency, functional dependence, dyspnea, chronic obstructive pulmonary disease, current smoking, congestive heart failure, bleeding disorder, ascites, cancer, steroid use, estimated glomerular filtration rate, hematocrit, procedure category, and log(operative time)

HR hazard ratio, *CI* confidence interval, *PAF* population attributable fraction

* $P < 0.0001$

[a] Confidence interval for PAF estimated using bootstrap technique

0.3%, the mortality was 54% in those with five or more complications.

Additive interaction of perioperative complications on 30-day mortality

Additive interaction was analyzed for the eight perioperative complications that were significant in multivariable analyses. All 28 combinations of two complications were assessed using Cox models, adjusted for preoperative comorbidities and risk factors (but not the other complications), and the criteria for statistical significance was modified using a Bonferroni correction ($\alpha = 0.05/28 = 0.0018$). Seven combinations of perioperative complications demonstrated significant positive additive interaction effects: (1) ARF–AKI, (2) ARF–sepsis/septic shock, (3) ARF–stroke, (4) AKI–sepsis/septic shock, (5) AKI–MI, (6) sepsis/septic shock-MI, and (7) sepsis/septic shock–cardiac arrest (Table 5). In addition, two combinations demonstrated significant negative additive interaction effects (ARF–cardiac arrest and cardiac arrest–transfusion). Of the combinations, the most common were ARF–sepsis/septic shock (1.1%), AKI–sepsis/septic shock (0.37%), and ARF–AKI (0.32%) (Table 6).

Sensitivity analysis: additive interaction of perioperative complications in high-risk intraabdominal general surgery patients

A sensitivity analysis determined whether the combination of complications with significant interaction effects was similar when analyzing a high-risk cohort of patients. Based on prior analyses [6], we removed patients from the following Clinical Classifications Software categories that were deemed to be low risk for complications and mortality: *appendectomy*, *cholecystectomy and common duct exploration*, *gastric bypass and volume reduction*, and *other hernia repair*, and the sensitivity cohort contained 208,750 records. In this high-risk cohort, there were no changes in the combination of complications demonstrating significant positive interaction effects, and cardiac arrest–transfusion was the only combination demonstrating significant negative additive interaction effects (Supplemental Table 3).

Discussion

We examined major perioperative complications in intraabdominal general surgery patients to determine those with synergistic effects on mortality. Of the eight

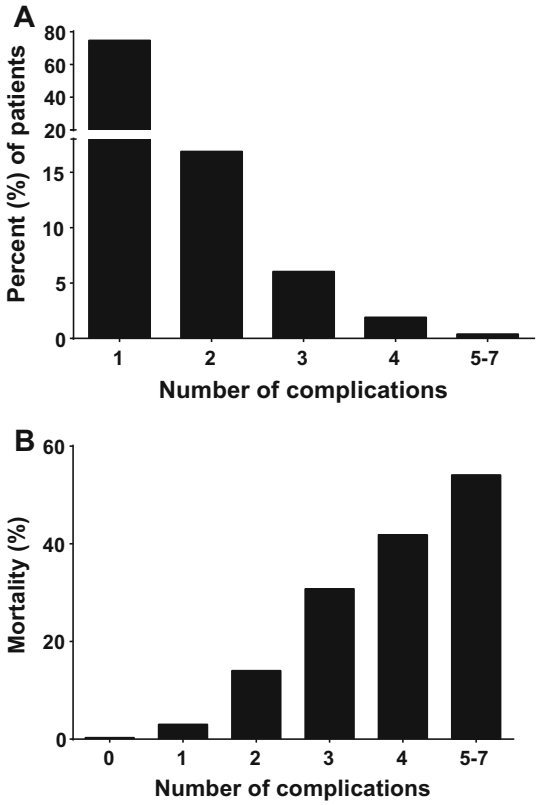

Fig. 1 Number of complications and mortality in patients undergoing intraabdominal general surgery procedures, American College of Surgeons National Surgical Quality Improvement Program, 2005–2011. Graphs depicting the distribution of patients developing at least one complication in patients undergoing intraabdominal general surgery **a** and the 30-day mortality of patients by number of complications **b**. A total of 43,486 (10%) patients developed at least one of the following eight complications: acute respiratory failure, acute kidney injury, cardiac arrest, deep vein thrombosis/pulmonary embolus, myocardial infarction, sepsis/septic shock, stroke, and/or transfusion; 379,341 (90%) patients did not develop any of these complications

complications analyzed, four demonstrated significant positive additive interaction effects with at least two others: (1) AKI, (2) ARF, (3) sepsis/septic shock, and (4) stroke. In addition, MI had positive interaction effects with AKI, while cardiac arrest had positive interaction effects with sepsis/septic shock but negative interaction effects with ARF and transfusion. Thus, certain perioperative complications had synergistic effects to affect the risk of postoperative mortality.

Perioperative complications are devastating events that lead to poor recovery and greater mortality in critically ill surgical patients. Much of the literature focuses on individual complications by examining risk factors for each and determining mortality rates for those with and without the complication [19–22]. However, complications do not occur in isolation and the relationships between them must be considered to fully understand the magnitude of their effects in the perioperative period. We previously demonstrated that the development of AKI, ARF, or sepsis/septic shock increased the risk of developing the other two complications and that multiple complications increased the risk of perioperative mortality in a synergistic manner [6]. These three specific complications were chosen because they frequently occur together in critically ill patients and have a common inflammatory response [23]. Here, we systematically analyzed a host of other major complications to determine whether any had synergistic relationships affecting mortality.

In addition to AKI, ARF, and sepsis/septic shock, stroke had positive interaction effects with ARF and sepsis/septic shock. Stroke is relatively uncommon after non-cardiovascular surgery [24], occurring in 0.2% of patients in our sample, but has a high mortality, being the complication with the third largest hazard for mortality (Table 3). Stroke may have several etiologies, including ischemia due to emboli and watershed zones [20], but may also originate from inflammatory causes [25], and there are known clinical interactions between stroke and other organ systems—including the kidney, lung, and heart—mediated by inflammation [26]. In addition, sepsis is frequently encountered in stroke patients that require care in a neurological intensive care unit (ICU) [27].

Cardiac arrest, occurring in 0.3% of patients, had the greatest mortality. Cardiac arrest might be expected to have positive interaction effects with most complications, and indeed, there were positive interaction effects with sepsis/septic shock. However, there were negative interaction effects with ARF and transfusion and the interaction with myocardial infarction, while not meeting the Bonferroni-adjusted criteria for statistical significance, was also negative, implying that for these complications, mortality was lower with the complication plus cardiac arrest than with cardiac arrest alone. Patients with complications may be monitored more carefully, such as in an ICU or stepdown unit, and are more likely to be resuscitated successfully after a cardiac arrest than those patients in a general surgical ward. Future studies will further delineate the specific relationships between cardiac arrest and other complications on surgical mortality.

Perioperative MIs occur due to either acute coronary syndrome or an imbalance between myocardial oxygen supply and demand [28]. MIs had significantly positive interaction effects on mortality with AKI, and it is known that worsening renal function after MI increases mortality risk [29, 30]. Interactions with several other complications (including ARF and sepsis), while not statistically significant, were, nevertheless, strongly suggestive of positive effects. Although DVT/PE and blood transfusions have inflammatory implications [31, 32], they were not involved

Table 5 Relative excess risk due to interaction from Cox models for 30-day mortality, adjusted for preoperative comorbidities, accounting for combinations of two perioperative complications in patients undergoing intraabdominal general surgery, American College of Surgeons National Surgical Quality Improvement Program, 2005–2011

	Acute Respiratory Failure				Acute Kidney Injury				Sepsis/Septic Shock			
		HR		95% CI		HR		95% CI		HR		95% CI
Acute Kidney Injury	ARF	19.3		[17.8, 20.8]								
	AKI	16.9		[14.4, 19.7]								
	ARF&AKI	85.7		[77.2, 95.0]								
	RERI	**50.5**	**	**[42.1, 59.0]**								
Sepsis/ Septic Shock	ARF	18.9		[17.2, 20.7]	AKI	16.8		[14.6, 19.4]				
	SEP	9.4		[8.51, 10.5]	SEP	11.0		[10.2, 11.9]				
	ARF&SEP	46.5		[42.8, 50.5]	AKI&SEP	60.7		[54.6, 67.5]				
	RERI	**19.2**	**	**[15.8, 22.5]**	RERI	**33.9**	**	**[27.7, 40.2]**				
Stroke	ARF	21.8		[20.3, 23.4]	AKI	20.6		[18.8, 22.5]	SEP	12.9		[12.1, 13.9]
	STR	11.4		[8.63, 15.0]	STR	11.0		[9.08, 13.4]	STR	12.1		[9.56, 15.2]
	ARF&STR	64.5		[51.1, 81.5]	AKI&STR	50.6		[33.0, 77.6]	SEP&STR	57.9		[43.9, 76.5]
	RERI	**32.3**	**	**[17.2, 47.4]**	RERI	19.9		-[1.72, 41.6]	RERI	**33.9**	**	**[17.7, 50.1]**
Cardiac Arrest	ARF	16.5		[15.3, 17.9]	AKI	23.2		[21.0, 25.6]	SEP	14.0		[13.0, 15.1]
	CA	294		[257, 336]	CA	172		[158, 187]	CA	218		[197, 240]
	ARF&CA	244		[223, 268]	AKI&CA	213		[180, 251]	SEP&CA	319		[284, 358]
	RERI	**-65.1**	**	**-[106, -24.5]**	RERI	18.3		[-17.4 54.0]	RERI	**88.1**	**	**[49.9, 126]**
Myocardial Infarction	ARF	22.1		[20.6, 23.7]	AKI	20.6		[18.8, 22.6]	SEP	13.3		[12.4, 14.2]
	MI	9.42		[7.57, 11.7]	MI	8.10		[6.93, 9.47]	MI	10.2		[8.56, 12.1]
	ARF&MI	39.3		[32.9, 46.8]	AKI&MI	52.2		[39.2, 69.5]	SEP&MI	32.2		[25.7, 40.2]
	RERI	8.75	*	[1.75, 15.7]	RERI	**24.5**	**	**[9.56, 39.4]**	RERI	9.71	*	[2.46, 17.0]
Deep Vein Thrombosis/Pulmonary Embolus	ARF	22.7		[21.1, 24.4]	AKI	21.1		[19.3, 23.1]	SEP	13.5		[12.6, 14.5]
	DVT	4.55		[3.77, 5.50]	DVT	4.10		[3.56, 4.72]	DVT	5.01		[4.22, 5.95]
	ARF&DVT	27.8		[23.4, 33.0]	AKI&DVT	26.6		[20.0, 35.3]	SEP&DVT	15.6		[13.0, 18.9]
	RERI	1.55		-[3.16, 6.26]	RERI	2.37		-[5.24, 10.0]	RERI	-1.89		-[4.90, 1.11]
Transfusion	ARF	25.6		[23.7, 27.8]	AKI	24.2		[21.8, 26.9]	SEP	14.6		[13.4, 15.8]
	TRA	2.04		[1.82, 2.28]	TRA	2.16		[1.97, 2.36]	TRA	2.28		[2.05, 2.53]
	ARF&TRA	24.1		[21.7, 26.8]	AKI&TRA	25.1		[21.8, 29.0]	SEP&TRA	17.8		[16.0, 19.9]
	RERI	-2.57	*	-[5.05, -0.09]	RERI	-0.25		-[4.18, 3.67]	RERI	2.00	*	[0.14, 3.87]

	Stroke				Cardiac Arrest				Myocardial Infarction			
		HR		95% CI		HR		95% CI		HR		95% CI
Cardiac Arrest	STR	12.4		[10.2, 15.0]								
	CA	142		[131, 153]								
	STR&CA	119.3		[72.4, 196]								
	RERI	-34.0		-[94.0, 26.0]								
Myocardial Infarction	STR	9.53		[7.89, 11.5]	CA	147		[135, 159]				
	MI	7.41		[6.42, 8.54]	MI	7.23		[6.12, 8.56]				
	STR&MI	36.3		[20.5, 64.2]	CA&MI	110		[87.2, 140]				
	RERI	20.3		-[0.43, 41.1]	RERI	-42.5	*	-[70.1, -14.9]				
Deep Vein Thrombosis/Pulmonary Embolus	STR	9.7		[8.06, 11.7]	CA	144		[133, 156]	MI	7.39		[6.38, 8.56]
	DVT	3.81		[3.34, 4.33]	DVT	3.82		[3.29, 4.43]	DVT	3.73		[3.26, 4.26]
	STR&DVT	19.8		[10.9, 35.9]	CA&DVT	134		[106, 169]	MI&DVT	16.7		[11.3, 24.9]
	RERI	7.30		-[4.61, 19.2]	RERI	-13.0		-[45.1, 19.2]	RERI	6.62		-[0.08, 13.3]
Transfusion	STR	12.4		[10.1, 15.3]	CA	190		[173, 207]	MI	8.29		[7.04, 9.8]
	TRA	2.23		[2.06, 2.42]	TRA	2.50		[2.28, 2.74]	TRA	2.21		[2.04, 2.41]
	STR&TRA	10.5		[7.34, 15.1]	CA&TRA	139		[121, 160]	MI&TRA	11.7		[9.07, 15.2]
	RERI	-3.14		-[7.67, 1.38]	RERI	**-52.0**	**	**-[75.1, -29.0]**	RERI	2.22		-[1.00, 5.44]

	Deep Vein Thrombosis/Pulmonary Embolus		
		HR	95% CI
Transfusion	DVT	4.68	[4.05, 5.42]
	TRA	2.29	[2.10, 2.49]
	DVT&TRA	4.90	[3.80, 6.33]
	RERI	-1.07	-[2.46, 0.32]

Each box contains estimates from separate adjusted Cox models that include parameters for patients developing either of two postoperative complications (row variable and column variable) or both complications simultaneously. The first three parameters are hazard ratios in the Cox model. The fourth parameter is the relative excess risk due to interaction for the combination of the two complications

In addition to the two postoperative complications, each Cox model also includes: age, female sex, white race, body mass index, emergency, functional dependence, dyspnea, chronic obstructive pulmonary disease, current smoking, congestive heart failure, bleeding disorder, ascites, cancer, steroid use, estimated glomerular filtration rate, hematocrit, procedure category, and log(operative time)

HR hazard ratio, *RERI* relative excess risk due to interaction, *CI* confidence interval, *ARF* acute respiratory failure, *AKI* acute kidney injury, *STR* stroke, *CA* cardiac arrest, *MI* myocardial infarction, *DVT* deep vein thrombosis/pulmonary embolus, *TRA* transfusion

** $P < 0.0018$ (Bonferroni-adjusted p-value.)

* $P < 0.05$

Table 6 Rates of two complication combinations with significant additive interactions, patients undergoing intraabdominal general surgery, American College of Surgeons National Surgical Quality Improvement Program, 2005–2011

Total sample	*N* 422,827	%
Positive interactions		
Acute respiratory failure–sepsis/septic shock	4670	1.1
Acute kidney injury–sepsis/septic shock	1544	0.37
Acute respiratory failure–acute kidney injury	1356	0.32
Sepsis/septic shock–cardiac arrest	519	0.12
Acute respiratory failure–stroke	175	0.04
Sepsis/septic shock–stroke	145	0.03
Acute kidney injury–myocardial infarction	119	0.03
Negative interactions		
Cardiac arrest–transfusion	376	0.09
Cardiac arrest–sepsis/septic shock	24	0.01

in significant positive interaction effects with other complications. These complications may have a relatively low impact on mortality compared to others, and the magnitude of interactions, if any, was small.

The majority of patients with complications developed only a single complication (75%) and mortality increased as the number of complications increased, regardless of the specific complication. While complications such as cardiac arrest were associated with extremely high increases in mortality risk, the overall effect of cardiac arrest on mortality was relatively small due to its low incidence. Indeed, the population attributable fraction associated with cardiac arrest was 0.30% [95% CI; 0.29%, 0.32%]. More common complications, such as sepsis/septic shock and transfusion, accounted for a greater percentage of mortality, with population attributable fractions of 2.8% [2.6%, 2.9%] and 1.4% [0.74%, 1.9%], respectively. Sepsis/septic shock was the most frequently involved in multiple complications, along with ARF and AKI.

This is a retrospective, observational study, and the dataset does not allow for the determination of the etiology of the complications or the specific causes underlying the observed interaction effects. A patient's perioperative clinical course is likely a combination of various factors—including biological, clinical, and social—that converge to determine their ultimate outcome. Major intraabdominal surgery can lead to altered hemodynamics from factors such as hypovolemia, hypotension, vasodilation with anesthetic agents, and mechanical obstruction of major vasculature leading to complications such as AKI and MI [19, 28]. In addition, surgery causes an inflammatory response that leads to an uncomplicated perioperative course in normal, well-balanced patients [33], but alterations in the normal physiological response due to factors such as preexisting comorbidities and perioperative complications can lead to an unbalanced response, causing systemic inflammation and multi-organ dysfunction.

Perioperative complications such as AKI, ARF, sepsis/septic shock, and stroke lead to inflammation and interactions with other organ systems [5, 20, 23, 25–27, 30, 31]. Clinical factors may play a role as the optimal treatment for injuries to different organ systems may often be in conflict. For instance, aggressive fluid management for AKI [34] or sepsis/septic shock [35] may lead to increased mortality. Finally, social factors, such as a "Do Not Resuscitate" order in critically ill patients [36] also likely contribute to the observed interaction effects.

Our study is subject to certain limitations, including those related to the retrospective study of large datasets [37]. In particular, the definitions of the specific outcomes are limited by the dataset and newer, more relevant criteria may not be used to define the outcomes. Many important variables, such as those related to intraoperative management, pharmacologic treatment, and admission to an ICU are not collected. In addition, the dataset does not identify specific hospitals or characteristics of hospitals so we do not know whether institutional factors, such as variations in failure to rescue [38], may account for our observed findings. Our sample includes various types of intraabdominal general surgery procedures, including those with low mortality risk, but a sensitivity analysis determined that the main inferences regarding the combinations of complications involved in significant interaction effects were not affected by the inclusion of these procedures.

In conclusion, a broad, epidemiologic assessment of major perioperative complications in intraabdominal general surgery patients found that in those developing multiple complications, certain complications–in particular

AKI, ARF, sepsis/septic shock, and stroke–had synergistic effects on 30-day mortality when combined with others. These observations should serve as the basis for further study to determine the biological (e.g., inflammatory response), clinical, and social mechanisms behind these interaction effects so that those patients at a high-risk for developing multiple complications may be properly identified and managed to prevent further adverse outcomes.

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