


# Clinical and Economic Burden Associated with Disruptive Surgical Bleeding: A Retrospective Database Analysis

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**Background:** Hemostatic agents are used to control surgical bleeding; however, some patients experience disruptive bleeding despite the use of hemostats. In patients receiving hemostats, we compared clinical and economic outcomes between patients with vs without disruptive bleeding during a variety of surgical procedures.

**Methods:** This was a retrospective analysis of the Premier Healthcare Database. Study patients were age  $\geq 18$  with a hospital encounter for one of 9 procedures with evidence of hemostatic agent use between 1-Jan-2019 and 31-Dec-2019: cholecystectomy, coronary artery bypass grafting (CABG), cystectomy, hepatectomy, hysterectomy, pancreatectomy, peripheral vascular, thoracic, and valve procedures (first procedure = index). Patients were grouped by presence vs absence of disruptive bleeding. Outcomes evaluated during index included intensive care unit (ICU) admission/duration, ventilator use, operating room time, length of stay (LOS), in-hospital mortality, and total hospital costs; 90-day all-cause inpatient readmission was also evaluated. Multivariable analyses were used to examine the association of disruptive bleeding with outcomes, adjusting for patient, procedure, and hospital/provider characteristics.

**Results:** The study included 51,448 patients; 16% had disruptive bleeding (range 1.5% for cholecystectomy to 44.4% for valve). In procedures for which ICU and ventilator use is not routine, disruptive bleeding was associated with significant increases in the risks of admission to ICU and requirement for ventilator (all  $p \leq 0.05$ ). Across all procedures, disruptive bleeding was also associated with significant incremental increases in days spent in ICU (all  $p \leq 0.05$ , except CABG), LOS (all  $p \leq 0.05$ , except thoracic), and total hospital costs (all  $p \leq 0.05$ ); 90-day all-cause inpatient readmission, in-hospital mortality, and operating room time were higher in the presence of disruptive bleeding and varied in statistical significance across procedures.

**Conclusion:** Disruptive bleeding was associated with substantial clinical and economic burden across a wide variety of surgical procedures. Findings emphasize the need for more effective and timely intervention for surgical bleeding events.

**Keywords:** health resource utilization, hospital costs, burden of bleeding, real-world evidence, RWE, hemostatic agent

## Introduction

Bleeding, a common intra- and post-operative surgical complication, may range from mild to severe in both its intensity and impact.<sup>1</sup> At the extreme, surgery-related bleeding increases mortality risk and has also been associated with increased use of high-intensity and expensive health-care services (eg, intensive care unit [ICU] admissions), longer operating times and hospital stays, elevated risk of a reoperation, and higher all-cause direct health-care costs.<sup>2-4</sup> A variety of hemostatic agents are routinely used to control bleeding during surgical procedures in hospitals in the United States; however, some patients experience disruptive bleeding despite the use of hemostats.<sup>2</sup> A previous study by Corral et al documented an association of disruptive bleeding with higher mortality risk, as well as greater healthcare resource use and total hospital costs among patients who had received a hemostatic agent during one of eight surgical procedures deemed by surgeons to carry substantial risk of

bleeding. However, the surgeries evaluated in that study were all performed via an open surgical approach and all in calendar year 2012; since that time, additional hemostatic agents have become available in the US and a systematic shift toward minimally invasive surgeries (MIS) has occurred.<sup>5-7</sup>

These fundamental changes in the surgical landscape suggest a need to revisit the question of how surgery-related disruptive bleeding may impact outcomes. Therefore, the current study was undertaken to examine the contemporary association of disruptive bleeding with healthcare resource utilization, in-hospital mortality, and total hospital costs among patients who received hemostats during selected surgical procedures. Consistent with the aforementioned analysis conducted by Corral et al, the procedures selected for study represent a wide variety of surgical specialties, including cardiovascular (coronary artery bypass graft, valve, and peripheral valve procedures), hepatopancreatobiliary/general surgery (hepatectomy, pancreatectomy, and cholecystectomy), gynecology (hysterectomy), thoracic (lung resection), and urology (cystectomy).<sup>2</sup>

## Materials and Methods

### Data Source

We conducted this retrospective observational study using electronic health record and hospital billing data from the Premier<sup>®</sup> Healthcare Database (PHD), Premier, Inc., NC, USA).<sup>8</sup> PHD is an all-payer, United States (US) population-based research database that contains inpatient and outpatient hospital billing records from over 900 hospitals and health systems that participated in the Premier Healthcare Performance Improvement Alliance at the time the data were obtained. The hospitals in the PHD are nationally representative with respect to bed size, geographic region, location (urban/rural) and teaching status. Source data include hospital discharge-level information on patient demographics, primary and secondary diagnoses, treatments (eg, procedures, medical devices/supplies, and medications), length of hospital stay, and discharge disposition, as well as information on facility and provider characteristics. For each encounter, the PHD also contains hospital cost data corresponding to a date-stamped log of all billed items by cost-accounting department. This analysis of the PHD was conducted under an exemption from Institutional Review Board oversight for US-based studies using de-identified health-care records, as dictated by Title 45 Code of Federal Regulations (45 CFR 46.101(b)(4)).<sup>9</sup>

### Patient Selection

We selected patients aged 18 years or older at the time of their first (index) inpatient or outpatient discharge for one of nine procedures of interest between January 1, 2019, and December 31, 2019: coronary artery bypass grafting (CABG), cholecystectomy, cystectomy, hepatectomy, hysterectomy, lung resection, pancreatectomy, peripheral vascular procedures (PVP), valve repair/replacement.

For the primary analysis, we included patients with evidence of hemostatic agent use during the index procedure; patients who met the other study selection criteria regardless of whether or not they had received a hemostatic agent were also examined in a sensitivity analysis. For both the primary and sensitivity analysis, we included only patients whose index procedure was performed at a hospital that contributed data to the PHD for at least 90 days post-discharge. We excluded patients whose index admission occurred through transfer from a different hospital, those with missing discharge status or sex, or those with zero or negative billed amounts for total, room and board, and/or supply costs.

### Measurement of Disruptive Bleeding and Outcome Variables

We classified each patient into one of two mutually exclusive cohorts based on the presence or absence of at least one event indicative of disruptive bleeding during the index procedure.<sup>2</sup> We identified disruptive bleeding events using the International Classification of Diseases, 10th Revision, Clinical Modification/Procedure Classification System (ICD-10-CM/PCS) diagnosis and procedure codes for hemorrhage or hematoma complicating a procedure and interventions to control bleeding; charges billed for use of hemovac drainage devices; charges billed for use of erythropoietin; blood product transfusions; and charges billed for cryoprecipitates, fresh frozen plasma, red blood cells, plasma, platelets, and whole blood. We required bleeding-related diagnoses to not be designated as

“present on admission”, an indicator that delineates conditions that were pre-existing upon admission vs those that were diagnosed acutely during the admission.

Outcomes evaluated during index included operating room time, intensive care unit (ICU) admission, ICU duration, ventilator use, length of stay, in-hospital mortality, and total hospital costs (ie, costs of the index admission from the hospital perspective); 90-day all-cause inpatient readmission was also evaluated.

## Measurement of Patient, Procedure, and Hospital/Provider Characteristics

In order to characterize the study cohort and adjust for underlying differences between patients with vs without disruptive bleeding in the analysis of outcomes, we measured the following characteristics during index: patients' age, sex, race/ethnicity, marital status, payer type (eg, Medicare, Medicaid, Commercial, and other), comorbidity burden as quantified by the Charlson Comorbidity Index (CCI) Score<sup>10</sup> and Elixhauser comorbidities;<sup>11,12</sup> surgical indication; hospital bed size, US Census region, urban vs rural location, teaching vs non-teaching status, procedure volume for the index procedure type under evaluation, and physician specialty.

## Statistical Analysis

We used generalized linear models (GLM) to quantify the association between disruptive bleeding and the study outcomes, adjusting for all patient, procedure, and hospital/provider characteristics described above. A log link and binomial error distribution were used for binary outcomes; a log link and negative binomial error distribution were used for count outcomes; a log link and gamma error distribution were used for total hospital costs. We conducted separate models for each of the nine types of index procedures. A *p*-value of  $\leq 0.05$  was used as the threshold for statistical significance. We performed all analyses with StataSE 16 (StataCorp, College Station, Texas, US).

## Results

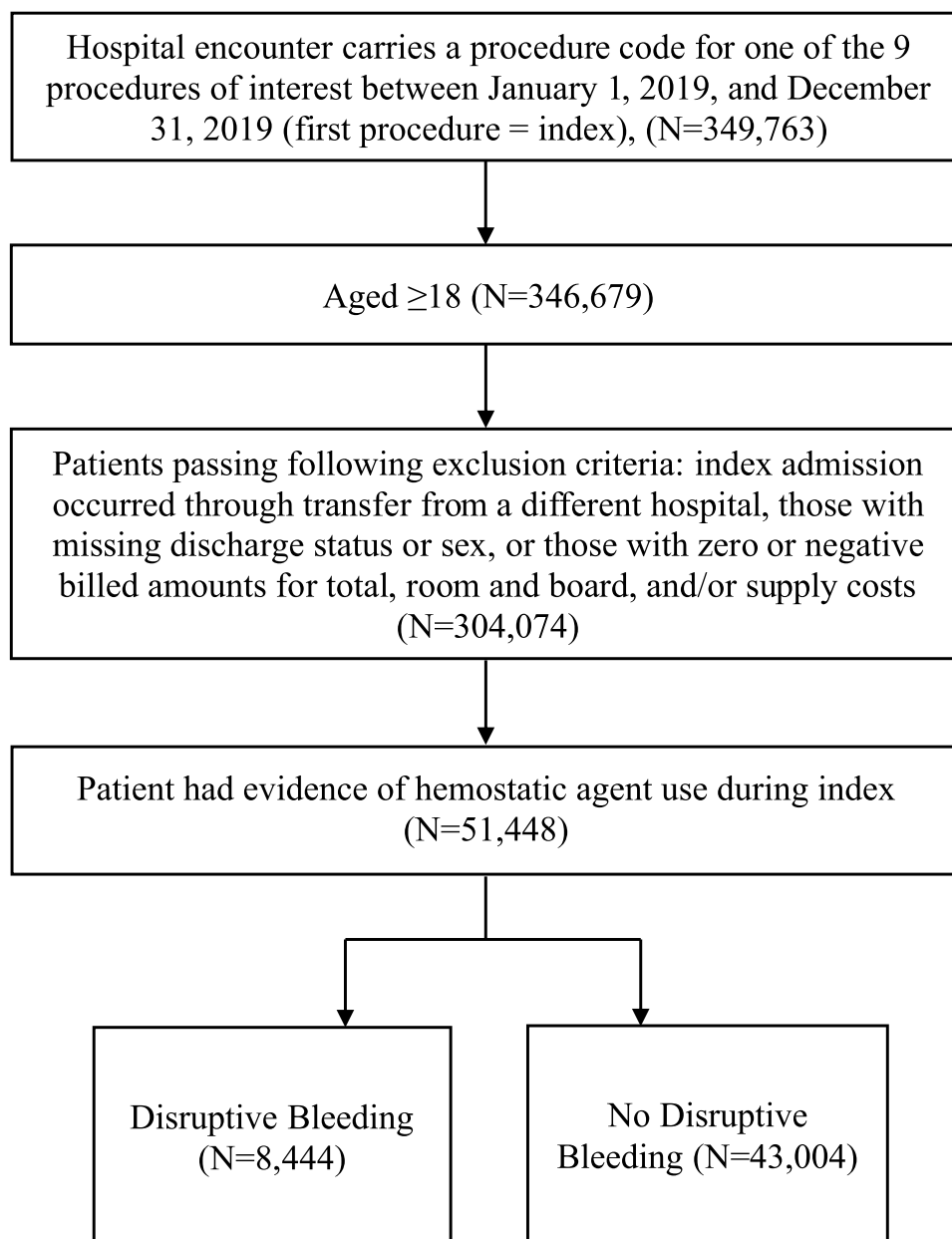
Figure 1 shows the sample size attrition associated with each step of patient selection. Among 349,763 patients with at least one hospital discharge for a procedure of interest in the 2019 calendar year, 304,074 patients met the final patient selection criteria for the broad sensitivity analysis population. Of these 304,074 patients, 51,448 patients had received a hemostatic agent during their index procedure and therefore contributed data for the primary analysis.

## Primary Analysis

Figure 2 shows patient counts and the incidence proportion of disruptive bleeding during the index admission for each of the nine procedures of interest. The number of patients included for the primary analysis ranged from 635 for cystectomy to 22,121 for hysterectomy. Overall, 8444 (16%) patients had disruptive bleeding during their index admission, while the remaining 43,004 patients had no evidence of disruptive bleeding. The incidence proportion of disruptive bleeding during index admission ranged from 1.5% of patients who underwent cholecystectomy to 44.4% of patients with valve procedures.

Table 1 shows selected patient characteristics, stratified by patients with vs without disruptive bleeding; these groups differed in terms of demographics, type of insurance coverage, and comorbidity burden. Compared with patients without disruptive bleeding, patients with disruptive bleeding were on average nearly 10 years older, more likely to be male, have Medicare coverage, and carried a greater comorbidity burden.

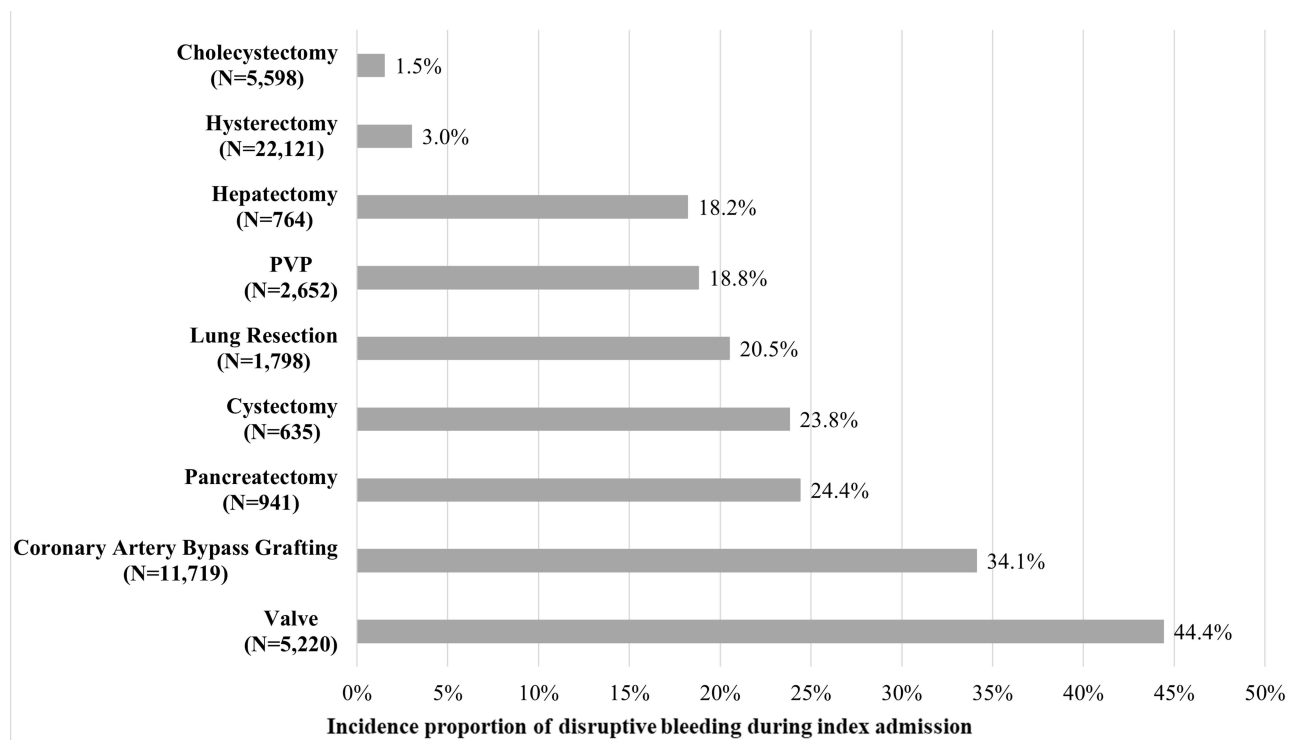
Table 2 shows the adjusted association of disruptive bleeding with mean operating room time, 90-day all-cause inpatient readmission rates, and inpatient mortality rates, stratified by index surgical procedure. Disruptive bleeding was associated with significantly longer operating room times for patients undergoing CABG, cholecystectomy, hepatectomy, hysterectomy, PVP, and valve procedures (incremental increases ranging from 22.6 minutes for CABG to 48.2 minutes for hepatectomy, all  $p \leq 0.05$ ). Disruptive bleeding was also associated with statistically significant increased risks of 90-day all-cause readmission for patients undergoing CABG, hepatectomy, hysterectomy, PVP, and valve procedures (incremental absolute risk increases ranging from 2.0% for hysterectomy to 16.1% for hepatectomy, all  $p \leq 0.05$ ).



**Figure 1** Patient selection.

Finally, disruptive bleeding conferred a substantial and significantly significant increase in the risk of inpatient mortality during the index admission for patients undergoing CABG, cystectomy, lung resection, pancreatectomy, and valve procedures (incremental absolute risk increases ranging from 1.0% for CABG to 28.4% for cystectomy, all  $p \leq 0.05$ ).

**Table 3** shows the adjusted association of disruptive bleeding with admission to ICU, duration of ICU stay, and ventilator use, stratified by index surgical procedure. With the exception of CABG and valve procedures, for which admission to ICU is routine, disruptive bleeding was associated with statistically significant increased risks of admission to ICU in all other procedures (incremental absolute risk increases ranging from 2.1% for hysterectomy to 20.4% for cystectomy, all  $p \leq 0.05$ ) and longer durations of ICU stay (incremental increases ranging from 0.3 days for hysterectomy to 1.6 days for cystectomy, all  $p \leq 0.05$ ). Disruptive bleeding was also associated with statistically significant higher risks of ventilator use among patients undergoing hepatectomy,



**Figure 2** Incidence proportion of disruptive bleeding during index admission.

hysterectomy, lung resection, pancreatectomy, and PVP procedures (incremental absolute risk increases ranging from 4.7% for hysterectomy to 21.3% for hepatectomy, all  $p \leq 0.05$ ).

Table 4 shows the adjusted association of disruptive bleeding with total hospital cost and length of stay for index admission, stratified by index surgical procedure. Disruptive bleeding was uniformly associated with statistically significant increases in total hospital costs for all procedures (incremental increases ranging from \$3329 for cholecystectomy to \$14,762 for valve procedures, all  $p \leq 0.05$ ), and increases in length of stay for all procedures except lung resection (incremental increases ranging from 1.4 days for CABG to 6.3 days for cholecystectomy, all  $p \leq 0.05$ ).

**Table I** Selected Patient Characteristics Among Patients in Whom a Hemostat Was Used

	No Disruptive Bleeding (N=43,004)	Disruptive Bleeding (N=8444)	P-value
Age, mean (SD)	55.8 (14.4)	64.7 (12.1)	<0.001
Sex, N (%)			<0.001
Female	29,844 (69.4%)	3257 (38.6%)	
Male	13,160 (30.6%)	5187 (61.4%)	
Race, N (%)			0.038
White	32,561 (75.7%)	6436 (76.2%)	
African American	4808 (11.2%)	923 (10.9%)	
Other	4631 (10.8%)	929 (11.0%)	
Unknown	1004 (2.3%)	156 (1.8%)	

(Continued)

**Table 1** (Continued).

	<b>No Disruptive Bleeding (N=43,004)</b>	<b>Disruptive Bleeding (N=8444)</b>	<b>P-value</b>
<b>Payer, N (%)</b>			<0.001
<b>Commercial</b>	20,932 (48.7%)	2288 (27.1%)	
<b>Medicaid</b>	4644 (10.8%)	693 (8.2%)	
<b>Medicare</b>	14,431 (33.6%)	4967 (58.8%)	
<b>Other</b>	2997 (7.0%)	496 (5.9%)	
<b>CCI score, mean (SD)</b>	1.5 (1.9)	2.9 (2.2)	<0.001
<b>CCI score, N (%)</b>			<0.001
<b>0</b>	19,270 (44.8%)	1178 (14.0%)	
<b>1–2</b>	14,206 (33.0%)	3150 (37.3%)	
<b>3–4</b>	5813 (13.5%)	2118 (25.1%)	
<b>5+</b>	3715 (8.6%)	1998 (23.7%)	

**Abbreviations:** CCI, Charlson Comorbidity Index; N, number; SD, standard deviation.

**Table 2** Adjusted Association of Disruptive Bleeding with Mean Operating Room Time, 90-Day All-Cause Inpatient Readmission Rates, and Inpatient Mortality Rates, Stratified by Index Surgical Procedure Among Patients in Whom a Hemostat Was Used

<b>Procedures</b>	<b>Operating Room Time</b>	<b>90-Day All-Cause Inpatient Readmission</b>	<b>Inpatient Mortality During Index Admission*</b>
	<b>Mean Minutes (95% CI)</b>	<b>Percentages (95% CI)</b>	<b>Percentages (95% CI)</b>
<b>CABG (N=11,719)</b>			
No disruptive bleeding	327.6 (315.7–339.4)	13.9% (12.9–14.9%)	1.1% (0.8–1.4%)
Disruptive bleeding	350.1 (334.4–365.9)	16.7% (15.4–18.0%)	2.1% (1.7–2.6%)
Incremental differences	22.6 (8.5–36.6)	2.8% (1.4–4.2%)	1.0% (0.5–1.5%)
p-value	0.002	<0.001	<0.001
<b>Cholecystectomy (N=5598)</b>			
No disruptive bleeding	113.7 (109.8–117.6)	5.6% (5.1–6.2%)	Insufficient N of events for model to converge
Disruptive bleeding	153.6 (138.2–169.)	7.1% (1.3–12.9%)	
Incremental differences	40.0 (24.5–55.4)	1.5% (–4.4–7.4%)	
p-value	<0.001	0.624	
<b>Cystectomy (N=635)</b>			
No disruptive bleeding	383.7 (355.3–412.1)	27.2% (23.7–30.6%)	Insufficient N of events for model to converge
Disruptive bleeding	387.7 (355.2–420.2)	25.7% (18.7–32.7%)	
Incremental differences	4.0 (–28.7–36.6)	–1.5% (–9.1–6.1%)	
p-value	0.812	0.708	

(Continued)

Table 2 (Continued).

Procedures	Operating Room Time	90-Day All-Cause Inpatient Readmission	Inpatient Mortality During Index Admission*
	Mean Minutes (95% CI)	Percentages (95% CI)	Percentages (95% CI)
<b>Hepatectomy (N=764)</b>			
No disruptive bleeding	296.0 (282.0–310.0)	13.1% (11.0–15.3%)	Insufficient N of events for model to converge
Disruptive bleeding	344.2 (323.2–365.2)	29.2% (21.2–37.2%)	
Incremental differences	48.2 (26.0–70.4)	16.1% (7.9–24.3%)	
p-value	<0.001	<0.001	
<b>Hysterectomy (N=22,121)</b>			
No disruptive bleeding	180.1 (173.8–186.4)	4.2% (3.9–4.5%)	0.1% (0.0–0.1%)
Disruptive bleeding	226.8 (215.6–238.0)	6.2% (4.5–7.9%)	0.8% (–0.6–2.2%)
Incremental differences	46.7 (37.2–56.3)	2.0% (0.3–3.7%)	0.7% (–0.7–2.1%)
p-value	<0.001	0.022	0.325
<b>Lung Resection (N=1798)</b>			
No disruptive bleeding	238.2 (227.1–249.3)	14.7% (12.8–16.5%)	1.1% (0.5–1.7%)
Disruptive bleeding	244.6 (204.8–284.4)	13.1% (9.8–16.3%)	6.6% (2.2–10.9%)
Incremental differences	6.4 (–35.8–48.6)	–1.6% (–5.4–2.2%)	5.5% (0.8–10.2%)
p-value	0.767	0.401	0.021
<b>Pancreatectomy (N=941)</b>			
No disruptive bleeding	389.0 (373.6–404.5)	29.9% (27.1–32.6%)	1.9% (0.9–3.0%)
Disruptive bleeding	393.3 (358.4–428.3)	30.9% (25.0–36.8%)	10.0% (4.9–15.1%)
Incremental differences	4.3 (–30.–38.6)	1.1% (–6.3–8.4%)	8.1% (2.7–13.5%)
p-value	0.806	0.777	0.003
<b>PVP (N=2652)</b>			
No disruptive bleeding	269.5 (256.7–282.3)	26.6% (25.0–28.2%)	1.4% (0.8–1.9%)
Disruptive bleeding	325.9 (311.1–340.8)	33.5% (29.7–37.2%)	1.8% (0.5–3.2%)
Incremental differences	56.5 (40.6–72.3)	6.9% (2.9–10.8%)	0.4% (–1.1–2.0%)
p-value	<0.001	0.001	0.566
<b>Valve Procedures (N=5220)</b>			
No disruptive bleeding	343.3 (329.8–356.9)	14.8% (13.5–16.1%)	2.4% (1.9–3.0%)
Disruptive bleeding	382.0 (367.4–396.7)	18.0% (16.1–20.0%)	4.7% (3.6–5.9%)
Incremental differences	38.7 (22.7–54.7)	3.2% (0.8–5.7%)	2.3% (1.0–3.6%)
p-value	<0.001	0.009	<0.001

**Notes:** \*Due to rarity of inpatient mortality, models were estimated among patients for whom the number of events per variable category were sufficient for convergence. Estimation sample sizes were: CABG=11,149; cholecystectomy=N/A; cystectomy=N/A; hepatectomy=N/A; hysterectomy=6975; lung resection=1282; pancreatectomy=941; PVP 2131; valve 5126.

**Abbreviations:** CABG, coronary artery bypass graft; CI, confidence interval; PVP, peripheral vascular procedures.

**Table 3** Adjusted Association of Disruptive Bleeding with Admission to ICU, Duration of ICU Stay, and Ventilator Use, Stratified by Index Surgical Procedure Among Patients in Whom a Hemostat Was Used

Procedures	Admission to ICU	ICU Stay	Ventilator Use
	Percentages (95% CI)	Mean Days (95% CI)	Percentages (95% CI)
<b>CABG (N=11,719)</b>			
No disruptive bleeding	93.8% (91.8–95.9%)	3.4 (3.1–3.7)	93.8% (92.5–95.1%)
Disruptive bleeding	93.7% (91.4–96.0%)	4.3 (3.9–4.6)	93.9% (92.0–95.7%)
Incremental differences	–0.1% (–1.9–1.7%)	0.8 (0.5–1.2)	0.0% (–1.4–1.4%)
p-value	0.927	0.927	0.953
<b>Cholecystectomy (N=5598)</b>			
No disruptive bleeding	Insufficient N of events for model to converge	Insufficient N of events for model to converge	Insufficient N of events for model to converge
Disruptive bleeding			
Incremental differences			
p-value			
<b>Cystectomy (N=635)</b>			
No disruptive bleeding	21.3% (15.9–26.7%)	2.1 (1.8–2.5)	7.4% (4.8–10.1%)
Disruptive bleeding	41.7% (30.4–53.0%)	3.8 (2.8–4.8)	13.2% (8.1–18.3%)
Incremental differences	20.4% (9.3–31.5%)	1.6 (0.5–2.8)	5.8% (–0.6–12.1%)
p-value	<0.001	<0.001	0.076
<b>Hepatectomy (N=764)</b>			
No disruptive bleeding	33.8% (28.5–39.1%)	2.6 (2.3–2.8)	5.6% (4.0–7.2%)
Disruptive bleeding	52.5% (40.2–64.8%)	3.7 (2.9–4.4)	26.9% (20.9–32.9%)
Incremental differences	18.7% (7.4–29.9%)	1.1 (0.3–1.9)	21.3% (14.8–27.7%)
p-value	<0.001	<0.001	<0.001
<b>Hysterectomy (N=22,121)</b>			
No disruptive bleeding	3.5% (2.8–4.3%)	2.9 (2.5–3.3)	1.2% (0.9–1.5%)
Disruptive bleeding	16.6% (12.8–19.2%)	3.2 (2.7–3.6)	5.9% (4.0–7.7%)
Incremental differences	12.5% (9.2–15.7%)	0.3 (–0.3–0.9)	4.7% (2.8–6.5%)
p-value	<0.001	<0.001	<0.001
<b>Lung Resection (N=1798)</b>			
No disruptive bleeding	48.1% (42.4–53.7%)	3. (2.6–3.3)	6.1% (4.7–7.5%)
Disruptive bleeding	57.7% (45.1–69.0%)	4.4 (3.6–5.3)	19.5% (13.5–25.6%)
Incremental differences	9.0% (–3.5–21.4%)	1.5 (0.6–2.4)	13.5% (7.0–19.9%)
p-value	0.160	0.160	<0.001
<b>Pancreatectomy (N=941)</b>			
No disruptive bleeding	43.1% (37.2–49.1%)	3.0 (2.7–3.4)	11.0% (8.4–13.7%)

(Continued)

**Table 3** (Continued).

Procedures	Admission to ICU	ICU Stay	Ventilator Use
	Percentages (95% CI)	Mean Days (95% CI)	Percentages (95% CI)
Disruptive bleeding	56.9% (50.0–63.8%)	3.9 (3.1–4.8)	22.7% (16.3–29.1%)
Incremental differences	13.8% (5.6–21.9%)	0.9 (0.0–1.7)	11.6% (4.5–18.7%)
p-value	<0.001	0.001	<0.001
<b>PVP (N=2652)</b>			
No disruptive bleeding	46.1% (41.5–50.8%)	2.5 (2.3–2.7)	5.9% (4.8–7.1%)
Disruptive bleeding	56.6% (49.8–62.2%)	3.5 (3.1–4.0)	12.5% (9.3–15.6%)
Incremental differences	9.9% (4.3–15.5%)	1.0 (0.6–1.5)	6.5% (3.5–9.6%)
p-value	<0.001	<0.001	<0.001
<b>Valve Procedures (N=5220)</b>			
No disruptive bleeding	93.4% (91.3–95.5%)	4.0 (3.7–4.3)	94.7% (93.2–96.2%)
Disruptive bleeding	95.5% (93.7–97.4%)	5.3 (4.9–5.7)	94.9% (93.4–96.4%)
Incremental differences	2.1% (0.4–3.8%)	1.3 (0.8–1.8)	0.2% (-1.7–2.1%)
p-value	0.013	0.013	0.836

**Abbreviations:** CABG, coronary artery bypass graft; CI, confidence interval; ICU, intensive care unit; PVP, peripheral vascular procedures.

**Table 4** Adjusted Association of Disruptive Bleeding with Total Hospital Cost and Length of Stay for the Index Admission, Stratified by Index Surgical Procedure

Procedures	Total Hospital Cost	LOS
	Mean (95% CI)	Mean Days (95% CI)
<b>CABG (N=11,719)</b>		
No disruptive bleeding	\$44,587 (\$42,544 – \$46,630)	8.5 (8.3–8.8)
Disruptive bleeding	\$54,091 (\$51,450 – \$56,731)	9.9 (9.6–10.3)
Incremental differences	\$9504 (\$7313 – \$11,695)	1.4 (1.1–1.8)
p-value	<0.001	<0.001
<b>Cholecystectomy (N=5598)</b>		
No disruptive bleeding	\$7176 (\$6891 – \$7461)	5.2 (4.7–5.7)
Disruptive bleeding	\$10,505 (\$9194 – \$11,815)	11.5 (6.8–16.2)
Incremental differences	\$3329 (\$2038 – \$4620)	6.3 (1.2–11.4)
p-value	<0.001	0.015
<b>Cystectomy (N=635)</b>		
No disruptive bleeding	\$34,604 (\$32,101 – \$37,108)	7.3 (6.8–7.8)
Disruptive bleeding	\$45,027 (\$39,429 – \$50,626)	11.4 (9.7–13.1)

(Continued)

Table 4 (Continued).

Procedures	Total Hospital Cost	LOS
	Mean (95% CI)	Mean Days (95% CI)
Incremental differences	\$10,423 (\$4502 – \$16,344)	4.1 (2.3–5.9)
p-value	0.001	<0.001
<b>Hepatectomy (N=764)</b>		
No disruptive bleeding	\$27,545 (\$25,835 – \$29,254)	5.5 (5.2–5.9)
Disruptive bleeding	\$41,612 (\$37,262 – \$45,962)	8.5 (7.4–9.6)
Incremental differences	\$14,067 (\$9318 – \$18,817)	3.0 (1.7–4.2)
p-value	<0.001	<0.001
<b>Hysterectomy (N=22,121)</b>		
No disruptive bleeding	\$11,067 (\$10,579 – \$11,555)	2.9 (2.8–3.0)
Disruptive bleeding	\$17,517 (\$15,942 – \$19,091)	4.6 (4.4–4.9)
Incremental differences	\$6449 (\$5117 – \$7782)	1.8 (1.5–2.1)
p-value	<0.001	<0.001
<b>Lung Resection (N=1798)</b>		
No disruptive bleeding	\$27,063 (\$25,692 – \$28,435)	6.1 (5.8–6.4)
Disruptive bleeding	\$36,749 (\$33,623 – \$39,875)	6.8 (5.5–8.1)
Incremental differences	\$9685 (\$6390 – \$12,981)	0.7 (–0.7–2.2)
p-value	<0.001	0.314
<b>Pancreatectomy (N=941)</b>		
No disruptive bleeding	\$35,394 (\$33,228 – \$37,560)	8.6 (8.1–9.1)
Disruptive bleeding	\$49,447 (\$43,644 – \$55,249)	12.0 (10.7–13.3)
Incremental differences	\$14,053 (\$8200 – \$19,905)	3.4 (2.0–4.8)
p-value	<0.001	<0.001
<b>PVP (N=2652)</b>		
No disruptive bleeding	\$26,460 (\$25,138 – \$27,782)	6.1 (5.8–6.4)
Disruptive bleeding	\$39,242 (\$36,497 – \$41,987)	9.3 (8.6–9.9)
Incremental differences	\$12,782 (\$10,237 – \$15,328)	3.2 (2.5–3.8)
p-value	<0.001	<0.001
<b>Valve (N=5220)</b>		
No disruptive bleeding	\$57,323 (\$54,702 – \$59,943)	9.0 (8.6–9.4)
Disruptive bleeding	\$72,085 (\$68,860 – \$75,309)	11.1 (10.6–11.5)
Incremental differences	\$14,762 (\$11,296 – \$18,228)	2.1 (1.4–2.7)
p-value	<0.001	<0.001

**Abbreviations:** CABG, coronary artery bypass graft; CI, confidence interval; LOS, length of stay; PVP, peripheral vascular procedures.

## Sensitivity Analysis of Broad Population

Results of sensitivity analysis in the broad population (ie, not restricted to patients with hemostatic agent use) are presented in the Supplement. As in the primary analysis, with few exceptions disruptive bleeding was associated with statistically significant increases in the risks or magnitude of all study outcomes.

## Discussion

This analysis of over 50,000 patients undergoing a wide variety of surgical procedures demonstrates the substantial clinical and economic burden associated with disruptive bleeding for US patients and hospitals.

The occurrence and impact of disruptive bleeding during routine surgeries has been studied previously, although the relevant literature is relatively sparse. Previous studies have provided somewhat more limited insights than the current study as they were often focused on a single type of procedure or specific geography/patient population (eg, critically ill patient), and all are based on older data and therefore they do not reflect the current surgical landscape.<sup>2-4,13-17</sup> The current study, for instance, shares a study design and data source common with the study published by Corral et al in 2015, but whereas that study included only open procedures, this study also included minimally invasive surgeries, a change made to better reflect the contemporary surgical landscape. Comparing results from these two studies suggests that there may have been some improvements in the procedure-specific incidence of disruptive bleeding in the intervening time. Specifically, the earlier study reported disruptive bleeding in 56% (versus 34%) of CABG patients, 68% (versus 44%) of cardiac valve surgery patients, 39% (versus 2%) of cholecystectomy patients, 60% (versus 24%) of cystectomy patients and 50% (versus 24%) in patients with pancreatic surgery. Not surprisingly, the incremental cost of bleeding is higher now than that previously reported for procedures that are still primarily performed using open approaches (ie, incremental costs reported in Corral et al vs current study for CABG: \$8910 vs \$9504; for cardiac valve procedures: \$13,286 vs \$14,762). For the procedures evaluated in both studies and which have recently largely shifted to minimally invasive approaches (eg, cholecystectomy, cystectomy, pancreatic surgery, and hysterectomy) the incremental cost of bleeding is from \$1888 to \$8289 lower than previously reported. Future studies may be designed to quantify temporal trends in the incidence and incremental costs of disruptive bleeding and to identify factors that shaped these trends, but it seems reasonable to suggest that improvements in surgical techniques, including an increasing array of hemostatic agents and greater use of minimally invasive approaches, have played a role.

A wide variety of hemostatic agents are available to clinicians, including those with mechanical, biological, and clot-forming properties, delivered through patches, sealants, and powders. A recent retrospective cost analysis by Ramirez et al estimated that the use of active hemostatic agents to reduce bleeds and the need for transfusions resulted in per-patient savings of \$19,472 by reducing blood product use in cardiac, thoracic, and ortho-ortho spine surgeries.<sup>17</sup> However, the present study suggests that even with the use of hemostatic agents, disruptive bleeding can occur with significant consequences. Although future investigation is needed to reveal the specific underlying factors that influence the risk of disruptive bleeding even with the use of hemostatic agents, the present study's findings suggest there may be room for improvement in terms of hemostatic agent choice optimization and more effective and timely intervention for surgical bleeding events.

## Limitations

As with any research study, an understanding of key data and/or design limitations provides important context for interpreting results. First, the selection of patients and measurement of many covariates and outcomes relied on diagnosis and procedure codes recorded within the PHD. Although these data are primarily recorded to support clinical and billing activity, they may be subject to measurement error. Second, in the primary analysis, all patients received hemostatic agents, suggesting that at least some amount of surgical bleeding took place to necessitate intervention. The classification of patients into the disruptive bleeding group relied on the presence of diagnoses, procedures, and use of products related to bleeding; although the documentation of such information may simply be reflective of the surgical bleeding that originally necessitated the use of a hemostatic agent, the significant association of disruptive bleeding with the study outcomes suggests that our classification was indeed a meaningful differentiator. Third, mortality is typically incompletely captured in real-world data sources, such as administrative claims and health systems data. This issue was mitigated by limiting our analysis to deaths that occurred during the facility visit for the index procedure. Although our results

provide an important perspective on the role of disruptive bleeding in shaping mortality risk, we acknowledge that the overall procedure-related mortality risk is likely greater than that reported here since some patients may die post-discharge. Fourth, drawing on a prior published definition,<sup>2</sup> we defined bleeding events based on a combination of diagnoses for hemorrhage or hematoma complicating a procedure, procedure codes for interventions to control bleeding, and use of other interventions such as hemovac drainage devices, erythropoietin, and blood products. As Premier Healthcare Database does not have information on the specific clinical indication for which the erythropoietin was used, it is possible that some uses may have been for indications aside from intra- or post-operative bleeding per-se; however, this accounted for a relatively small number of patients (N=937 across all surgical procedures) and therefore over-identification of bleeding events would likely be minimal and potentially offset by false-negative instances of bleeding (ie, bleeding occurred but was not clinically documented). On balance, it is unlikely that the estimated incremental burden associated with disruptive bleeding would be heavily influenced by inclusion or exclusion of these cases. Finally, we note that PHD is an all-payer database that is generally considered nationally representative of US hospitals; however, the present results may not necessarily generalize to all hospitals or international settings.

## Conclusions

The incidence of disruptive bleeding among patients in whom a hemostat was used varied by procedure type and was associated with substantial clinical and economic burden across a wide variety of surgical procedures. These findings emphasize the need for more effective and timely intervention for surgical bleeding events.

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SSJ and WD are employees and stockholders of Johnson & Johnson. PT is an employee of Mu Sigma. MA and PT provided data and analysis support under contract to Johnson & Johnson. The authors report no other conflicts of interest in this work.

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