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ORIGINAL RESEARCH

Health and economic outcomes associated with uncontrolled surgical bleeding: a retrospective analysis of the Premier Perspectives Database

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Background: Bleeding remains a common occurrence in surgery. Data describing the burden of difficult-to-control bleeding and topical absorbable hemostat use are sparse. This study was conducted to estimate the clinical and economic impact that remains associated with uncontrolled surgical bleeding, even when hemostats are used during surgery.

Methods: This US retrospective analysis used the Premier Perspectives Database. Hospital discharges from 2012 were used to identify patients treated with hemostats during eight surgery types. Patients were included if they were ≥18 years, had an inpatient hospitalization with one of the eight surgeries, and received a hemostat on the day of surgery. Patients were stratified by procedure and presence or absence of major bleeding (uncontrolled) despite hemostat use. Outcomes were all-cause hospitalization costs, hemostat costs, length of stay, reoperation, and surgery-related complications (eg, mortality). Statistical significance was tested through chi-square or *t*-tests. Multivariate analyses were conducted for all-cause costs and length of stay using analysis of covariance.

Results: Among 25,048 procedures, major bleeding events occurred in 14,251 cases. Despite treatment with hemostats, major bleeding occurred in 32%–68% of cases. All-cause costs were significantly higher in patients with uncontrolled bleeding despite hemostat use versus controlled bleeding (US$24,203–$61,323 [uncontrolled], US$14,420–$45,593 [controlled]; $P<0.001$). Hemostat costs were significantly greater in the uncontrolled bleeding cohort for all surgery types except cystectomy and pancreatic surgery. Reoperation and mortality rates were significantly higher in the uncontrolled bleeding cohort in all surgical procedures except cystectomy and radical hysterectomy.

Conclusion: Uncontrolled intraoperative bleeding despite hemostat use is prevalent and associated with significantly higher hospital costs and worse clinical outcomes across several surgical procedures compared to controlled bleeding. There is an unmet need for newer hemostats that can more effectively control bleeding, improve outcomes, and reduce hospital resource use.

Keywords: hemostat, costs, bleeding, Premier, surgery, burden

Background

Intraoperative and postoperative bleeding remains a common major complication of surgery.[1–5] An aging population with growing comorbidities and high anticoagulant use are important factors that contribute to high surgical bleeding risks.[6–8] Surgical bleeding can range from mild or moderate in intensity to severe or traumatic. There are a number of conventional surgical methods (eg, suture, ligature, compression, and cautery) and topical absorbable hemostats (TAHs) available to achieve hemostasis in mild to moderate bleeding scenarios.[9–13] Hemostatic agents in particular have become a growing treatment option over the past couple of decades, and have been associated with improved surgical and clinical outcomes.[14]

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Mild or moderate surgical bleeding may be straightforward to manage; however, bleeding may also be problematic or difficult to control, depending on several factors including bleeding severity, visibility and access to the bleeding source, anatomic location of the bleeding, patient coagulation status, and surgical skill.[12] These types of bleeding scenarios are often referred to in the literature using several common bleeding terms including severe,[1] major,[5] or excessive.[15] For example, diffuse bleeding from broad surface areas in patients who are coagulopathic may be particularly difficult to manage which may lead to additional procedures such as blood transfusion.[9,12] Traumatic bleeding may be placed at the top of this spectrum where patients have severe bleeding from injured tissues and often traditional methods of hemostasis are ineffective, necessitating multiple units of transfused blood.[16,17]

In more problematic and difficult bleeding, there is often no single solution that can allow surgeons to rapidly stop bleeding.[18–20] As a result, these situations often involve combinational use of hemostatic products in addition to conventional methods, which may be cumbersome, time-consuming, and costly.[12,21] Furthermore, several studies describe the substantial clinical and economic burden with such bleeding.[15,16,22–24] Bleeding can lengthen, interrupt, or complicate the surgery as well as increase likelihood of transfusion, reoperation, and associated complications.[22,25–28] Furthermore, it has been reported that severe, excessive, or uncontrolled bleeding during surgery can increase mortality rates to 20%.[1,3] It has also been estimated that uncontrollable bleeding accounts for approximately 40% of trauma-related deaths.[29]

Despite available data describing the burden of difficult or uncontrollable bleeding, there is still a need to understand how hemostat use impacts the incidence of such bleeding, and the risk of associated complications. Currently, no studies have explicitly assessed the burden of surgical bleeding in relation to hemostat use. Consequently, this retrospective analysis of the Premier database was conducted to estimate the hospital resources and costs that remain associated with uncontrolled surgical bleeding, even when hemostatic agents are used during surgery.

Methods

Study design and data source

A retrospective analysis was conducted using data from the Premier Perspectives Database (PPD). Information contained within the PPD is de-identified making it fully compliant with the Health Insurance Portability and Accountability Act (HIPAA). The PPD includes data on more than 600 participating hospitals and 47 million hospital discharges in the US. Participating hospitals submit data on patient demographic and payer information as captured on the hospital billing record. Before the information is added to the database, all data go through quality assurance and validation checks. Available data include all billed items by the cost-accounting department, including medications; laboratory, diagnostic, and therapeutic services; and primary and secondary diagnoses for each patient. Further, hospital information, such as geographical location, bed size, and teaching hospital status, is also included within the PPD.

Patient population

All hospital discharges with admission dates in 2012 were used to identify patients who were treated with hemostatic agents during select surgeries. Eight major surgeries were selected that were deemed by surgeons to be commonly associated with major bleeding and included cardiac revascularization, cardiac valve surgery, cholecystectomy, cystectomy, pancreatic, partial hepatic resection, pulmonary, and radical abdominal hysterectomy. Surgeries of interest were identified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) procedure codes (Table S1). Specific hemostatic agents used in surgery included mechanical, thrombin, flowable, and fibrin sealant agents (Table S2). Patients were identified for inclusion if they were admitted to a hospital in 2012, underwent an inpatient surgery of interest as the primary procedure, and received a hemostatic agent on the day of the surgery. Patients were excluded if they were less than 18 years old or had received an additional major surgical procedure on a different body system on the same day as the index procedure. For patients with multiple hospitalizations, only the first was included for analysis.

Major bleeding events

Within each of the eight surgery subgroups, patients were further stratified by the presence or absence of a major bleeding (ie, uncontrolled bleeding) event despite hemostat use. Major bleeding events were identified by following the ICD-9-CM diagnosis and procedure codes: hemorrhage or hematoma complicating a procedure (998.11 and 998.12); interventions to control bleeding (34.09, 39.98, 44.44, 44.49, 54.19, 39.41, 34.03, 54.12, 57.93); charges billed for use of hemovac drainage devices; charges billed for use of erythropoietin; blood product transfusions (99.00–99.09); and charges billed for cryoprecipitates, fresh frozen plasma, red blood cells, plasma,

platelets, and whole blood. A detailed listing of these major bleeding events is outlined in Table S3.

Study outcomes

The main study outcomes included in the study were the all-cause costs incurred during hospitalization, the cost of hemostatic agents, length of stay (LOS) between surgery and discharge, intensive care unit (ICU) stay, operation time, reoperation, and potential surgery-related complications (eg, mortality, infection, transfusions, ventilator use). Total all-cause costs included room and board, surgery, professional fees, supplies, pharmacy services, and laboratory services. Reoperation was defined as procedures on the same body system as the original procedure, performed during the same hospitalization. Additionally, both infections and transfusions were defined according to specific ICD-9-CM codes, which are summarized in Tables S4 and S5, respectively. Other study measures included were patient demographics, payment source, admitting hospital characteristics, type of hemostatic agents used (eg, mechanical, active, flowable, fibrin sealant), and the all payer refined-diagnosis related groups (APR-DRGs). The APR-DRG simultaneously evaluates the interactions of multiple comorbidities, age, and primary and secondary discharge diagnoses.

Statistical analyses

All data transformations and statistical analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC, USA). Patient demographics and hospital characteristics were evaluated for all surgical subgroups combined. Descriptive statistics (eg, means, patient counts) were stratified by the presence or absence of major (ie, uncontrolled) bleeding events. All statistical analyses on outcome measures were conducted separately for each surgical subgroup. Chi-square or *t*-tests were used to test for statistical significance whenever applicable; all tests were two-sided with a significance level of 0.05. Multivariate analyses were conducted to compare all-cause costs and LOS between patients with and without uncontrolled bleeding. Patient demographics and admitting hospital characteristics thought to have an impact on costs and LOS were included into the multivariate analysis, including age, race, sex, payment source, hospital geographic region, hospital location (rural vs urban), surgical admission type (elective vs emergent), teaching hospital status, and bed size. Analysis of covariance (ANCOVA) was used to adjust for these baseline characteristics.

Results

A total of 50,696 patients were identified within the Premier database that underwent a selected surgery in 2012, of which 25,155 were excluded because no hemostatic agent was used during surgery (Figure 1). Of the remaining 25,541 patients, 125 were excluded as they were younger than 18 years, and 368 were further excluded because they required additional surgery on a different body system on the same day. Thus, 25,048 patients were included in the analysis (cardiac revascularization: 12,799; cardiac valve surgery: 8,016; cholecystectomy: 1,576; cystectomy: 423; pancreatic: 464; partial hepatic: 620; pulmonary: 954; radical abdominal hysterectomy: 196).

Patient demographics and admitting hospital characteristics are presented in Tables 1 and 2. There were some notable differences between controlled and uncontrolled bleeding patients. In particular, there was a larger percentage of urgent cases in the uncontrolled versus controlled bleeding group (ie, 52% vs 40%), as well as a higher proportion of extreme APR-DRG disease severity in uncontrolled versus controlled bleeding (ie, 28% vs 8.4%).

Among 25,048 procedures, 14,251 uncontrolled bleeding events were recorded. The prevalence of uncontrolled bleeding events within each surgical subgroup is presented in Figure 2. Despite the use of hemostatic agents, uncontrolled bleeding events occurred in 32%–68% of patients, depending on the type of procedure. The most common type of event was use of a blood product, which occurred in 49.0% of all patients. Within the uncontrolled bleeding cohort, 25%–71% of patients required transfusions, with 5.8%–32.8% of patients receiving platelets, and up to 3.2% receiving coagulation factors. By definition, patients in the controlled bleeding cohort did not require transfusions.

Mortality for each surgical subgroup, stratified by the presence of uncontrolled bleeding despite hemostat use, is presented in Figure 3. Mortality was statistically significantly higher in the uncontrolled versus controlled bleeding cohort in all surgical subgroups except cystectomy and radical hysterectomy. Mortality rates ranged from 1.2% to 7.3% for uncontrolled bleeding and 0% to 1.2% for controlled bleeding cohorts.

Results pertaining to hospital resource use and costs are presented in Tables 3 and 4 for each surgical group, stratified by the presence or absence of uncontrolled bleeding despite hemostat use. All-cause costs were statistically significantly greater in patients with uncontrolled bleeding versus controlled bleeding for all surgery subgroups (uncontrolled bleeding: US$24,203–$61,323 vs controlled

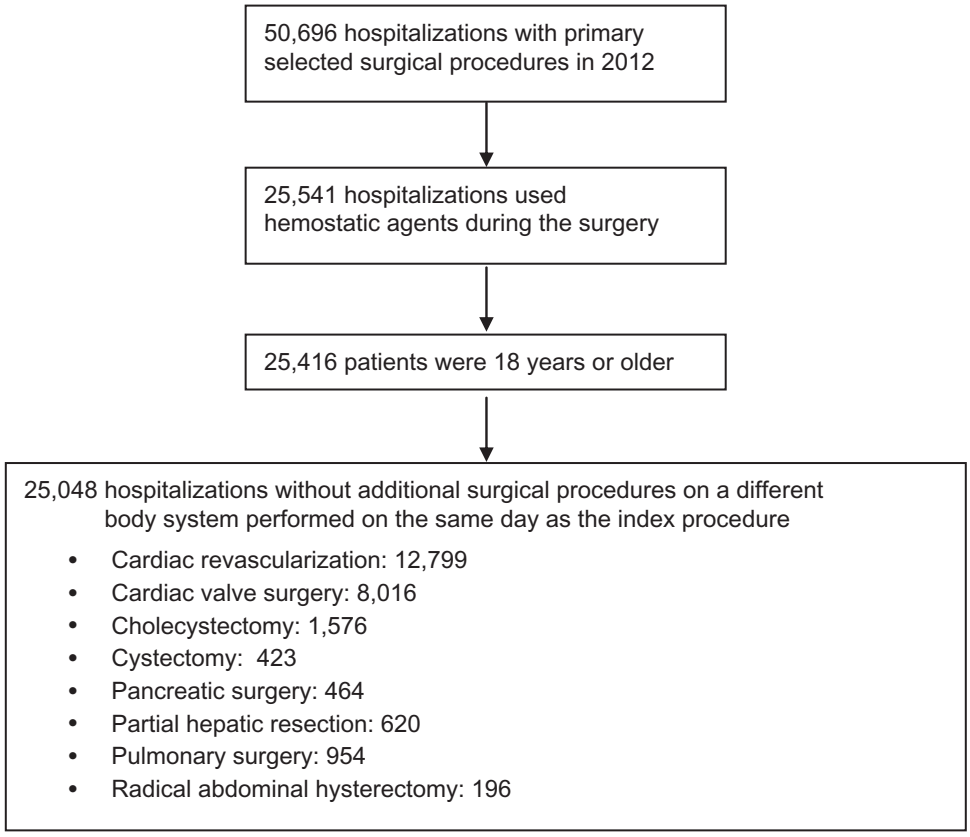


Figure 1 Patient identification flow chart.

bleeding: US$14,420– $45,593; $P<0.001$). Similarly, LOS was also statistically significantly greater with uncontrolled bleeding patients for all subgroups (uncontrolled bleeding: 7.1–17 days vs controlled bleeding: 4.1–10 days; $P<0.001$). After adjusting for baseline differences, results for all-cause costs and LOS were consistent with unadjusted values (Table 4).

The cost of hemostatic agents was also statistically significantly greater in the uncontrolled bleeding cohort for all surgical groups, except pancreatic surgery and cystectomy (uncontrolled bleeding: US$287–$799 vs controlled bleeding: US$203–$451) (Table 3). Furthermore, ICU stay and infection were always statistically significantly greater in the uncontrolled versus controlled bleeding cohorts, across surgery subgroups. Reported infections included urinary tract infections, septicemia, fever, and pneumonia. Reoperation rates were also statistically significantly greater in uncontrolled bleeding patients, with the exception of radical abdominal hysterectomy. Ventilator use was also more common in uncontrolled bleeding in all surgery cohorts except cystectomy. Finally, operating time was typically higher in uncontrolled versus controlled bleeding cohorts by 13.3–37.6 minutes, but differences were only statistically significant for cardiac revascularization, cardiac valve surgery, pulmonary surgery, and radical hysterectomy (Table 3).

Discussion

Using a sample of over 25,000 patients, we found that a substantial proportion of patients have uncontrolled surgical bleeding despite current hemostat use, with rates ranging from 32% to 68% depending on the procedure. Both infection rate and mortality were statistically significantly higher for uncontrolled versus controlled bleeding cohorts for all surgery types. Resource use, including length of hospital stay, ICU stay, ventilator use, operation time, and reoperation were often higher in patients with uncontrolled bleeding. These results were consistent with adjusted all-cause costs, which were always significantly greater in uncontrolled versus controlled bleeding cohorts.

Several studies have reported on the risk of surgical bleeding; however, reported rates span a wide range, which may be due to varying definitions of bleeding, differences in study design and geographic location, as well as variations in surgical procedures studied.[1,5,15,24] For example, a recent study by Dyke et al[1] reported a major (ie, moderate or severe/massive) bleeding rate of 33.8% in cardiac surgery. Classification

Table 1 Baseline patient demographics and admitting hospital characteristics

1.1	Bleeding not controlled despite hemostat use (N=14,251)	Bleeding controlled with hemostat (N=10,797)	*P*-value
Age, mean (SD)	67 (11.9)	63.9 (12.0)	<0.001
Female, N (%)	5,359 (37.6)	3,143 (29.1)	<0.001
Race, N (%)			<0.001
White	10,541 (74.0)	7,983 (73.9)	
Black	1,085 (7.6)	702 (6.5)	
Other	2,625 (18.4)	2,112 (19.6)	
Payment source, N (%)			<0.001
Managed care/ commercial	3,373 (23.7)	3,642 (33.7)	
Medicare	8,817 (61.9)	5,517 (51.1)	
Other	2,061 (14.5)	1,638 (15.2)	
Admission type, N (%)			<0.001
Elective	6,840 (48.0)	6,469 (59.9)	
Urgent/emergent	7,411 (52.0)	4,328 (40.1)	
Type of hemostatic agent, N (%)			<0.001
Active	1,774 (12.4)	1,604 (14.9)	
Fibrin sealant	2,287 (16.0)	1,401 (13.0)	
Mechanical	5,295 (37.2)	5,057 (46.8)	
Multiple categories*	4,895 (34.3)	2,735 (25.3)	
APR-DRG disease severity, N (%)			<0.001
Minor	593 (4.2)	1,196 (11.1)	
Moderate	3,582 (25.1)	4,812 (44.6)	
Major	6,040 (42.4)	3,884 (36.0)	
Extreme	4,036 (28.3)	905 (8.4)	

Note: *More than one hemostat used per patient.
Abbreviations: N, number of patients; SD, standard deviation; APR-DRG, all payer refined-diagnosis related groups.

Table 2 Hospital characteristics

1.2	Bleeding not controlled despite hemostat use (N=14,251)	Bleeding controlled with haemostat (N=10,797)	*P*-value
Hospital region (US), N (%)			<0.001
Northeast	3,057 (21.5)	1,848 (17.1)	
Midwest	1,829 (12.8)	2,382 (22.1)	
West	2,177 (15.3)	2,210 (20.5)	
South	7,188 (50.4)	4,357 (40.4)	
Teaching hospital, N (%)			<0.001
Yes	8,178 (57.4)	5,488 (50.8)	
No	6,073 (42.6)	5,309 (49.2)	
Location of hospital, N (%)			<0.001
Rural	1,176 (8.3)	1,206 (11.2)	
Urban	13,075 (91.7)	9,591 (88.8)	
Bed size, N (%)			<0.001
<750	10,903 (76.5)	9,428 (87.3)	
750+	3,348 (23.5)	1,369 (12.7)	

Abbreviation: N, number of patients.

of major bleeding in this study depended on the amount of total blood loss, transfusion units, need for surgical re-exploration, and whether there was delayed sterna closure. This rate is reportedly lower than the observed rate of 56%–68% in cardiac revascularization or valve surgery in this study. Another study by Stone et al[5] reported a major bleeding rate in the US cardiac surgery patients of 52.9% where the bleeding definition encompassed decrease in hemoglobin levels, reoperation for bleeding, access site hemorrhage requiring intervention, ≥5 cm hematoma, or transfusion. Other studies reported major or excessive bleeding rates of lower than 10%; however, those studies used a more restrictive definition, which specified the number of transfusion units needed to qualify under the bleeding definition[24] or the amount of postoperative bleeding drainage in cardiac surgery.[15] Our study included more liberal definitions of uncontrolled bleeding as well as several additional surgery types relative to these latter studies. Also, our study included eight surgery types deemed by surgeons to be commonly associated with major bleeding. Furthermore, unlike our study which focused solely on surgeries involving hemostat use, it is unclear to what extent hemostats were used in most of these published studies reporting bleeding risk.

These current study findings are aligned with studies that have quantified resource use and costs associated with surgical bleeding. An earlier 2011 US study by Stokes et al[23] reported that patients with bleeding-related complications (eg, transfusions) across different surgery types had significantly greater hospital costs and longer LOS. Our current study adds additional granularity in the types of resources comprising greater hospital costs in uncontrolled bleeding patients, such as reoperation, infection treatment, and ICU stay. Further, our study uniquely shows that these additional resources and costs are still high despite single or multiple hemostat product use. From the European perspective, Christensen et al[15] demonstrated that hospital costs and resources including ICU stay, ventilator, and reoperation were significantly higher in patients with excessive postoperative bleeding compared to patients without.

The uptake of hemostats has been rapid over the last several years. A study by Wright et al[14] showed that hemostat use continues to rise even for surgical procedures that are associated with very low bleeding complication and transfusion risk. Reviews of randomized trials demonstrate that hemostats can improve hemostasis and certain resource outcomes (eg, transfusions); however, benefits may vary by patient population type and hemostat product used.[30–34] In surgical situations where bleeding is more difficult to

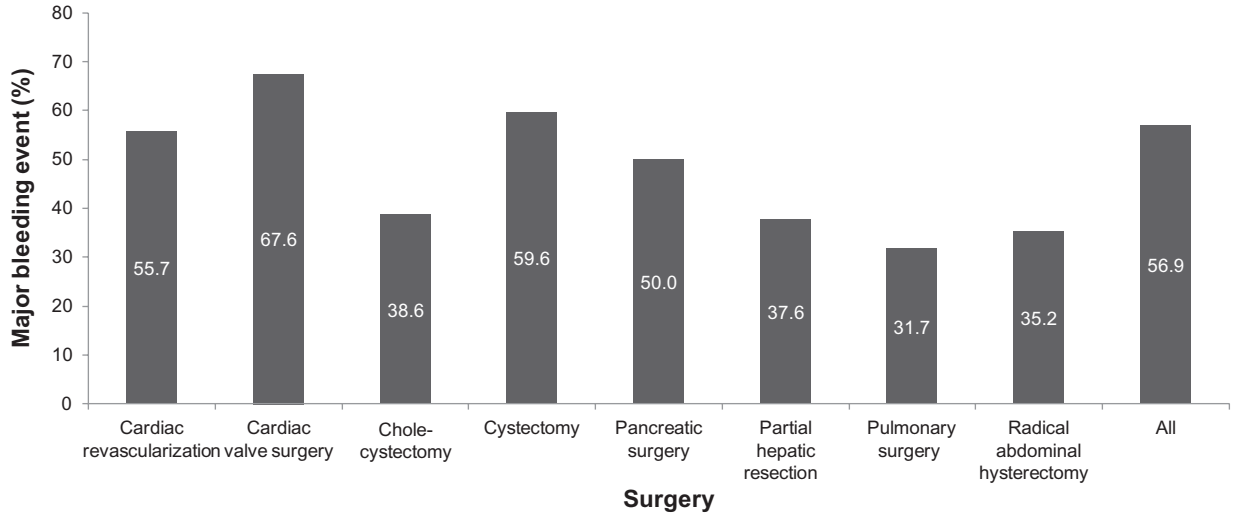


Figure 2 Percentage of patients with a major bleeding event despite hemostat use, stratified by surgery group.
Notes: Major bleeding (ie, uncontrolled bleeding) events were defined as: hemorrhage or hematoma complicating a procedure; interventions to control bleeding; charges billed for use of hemovac 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.

control, combined use of multiple hemostats is sometimes undertaken to try to achieve hemostasis.[12,21] In our study, hemostat costs have been observed to be significantly higher in patients with uncontrolled bleeding, which may be partially explained by more combination hemostat use. Despite these additional hemostat costs, uncontrolled bleeding rates and associated resource use remained high, signifying the suboptimal benefit that some currently approved hemostats may have. Limitations with such hemostats, including insufficient adhesion strength, lack of efficacy in a wet field, and inability to withstand forces of brisk hemorrhage, may explain the continued risk of uncontrolled bleeding in many surgery types.[9,12,18–20]

To address the prevalent problem of difficult-to-control surgical bleeding, a multifaceted approach is required. Essentially, methods to better assess appropriateness of operation technique and use of the various surgical methods for hemostasis are needed. Optimizing the use of right hemostatic technique (or product) with the right procedure can be an important goal for continuing education. Furthermore, new hemostats becoming available on the market that are targeted to problematic bleeding situations may help to

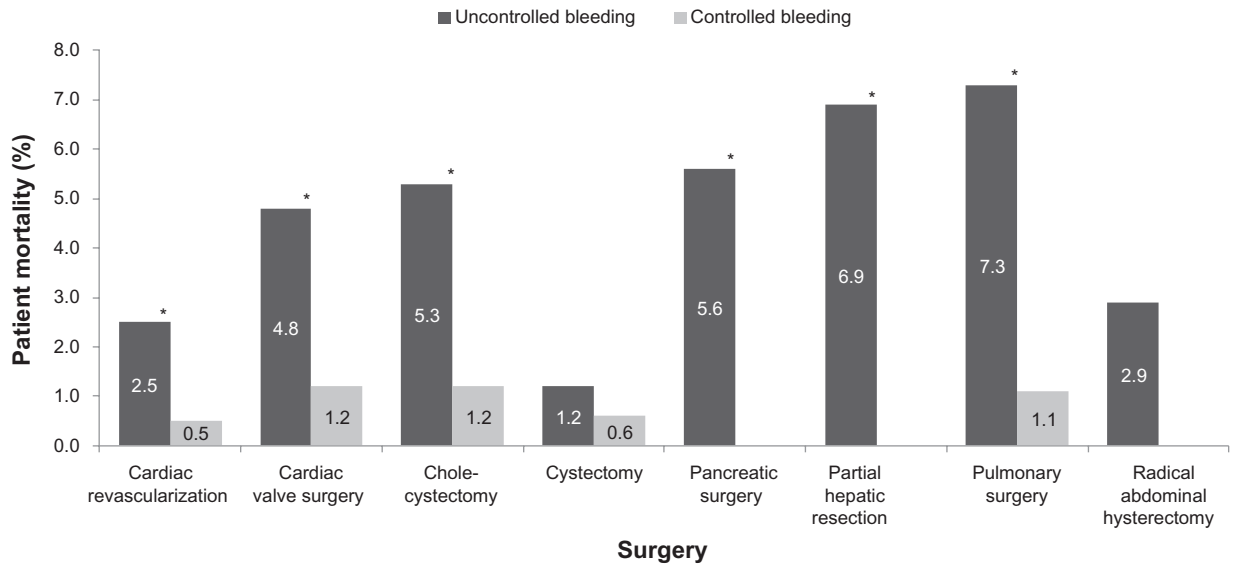


Figure 3 Patient mortality, stratified by surgery type and presence or absence of uncontrolled bleeding despite hemostat use.
Note: *Statistically significant ($P<0.001$).

Table 3 Unadjusted mean (SD) costs and resource use, stratified by surgical procedure and presence or absence of uncontrolled bleeding despite hemostat use

Surgery type	All-cause cost, US$ (SD)	Cost of hemostatic agent, US$ (SD)	LOS, days (SD)	ICU stay, days (SD)	Operation time, minutes (SD)	Reoperation, N (%)	Infection, N (%)	Ventilator use, N (%)
Cardiac revascularization								
Uncontrolled	44,327 (30,565)	406 (531)	7.8 (6.4)	5.7 (6.4)	332.3 (129.0)	989 (13.9)	1,818 (25.5)	6,841 (95.9)
Controlled	35,125 (17,601)	254 (329)	5.7 (3.4)	3.6 (3.8)	312.5 (143.5)	372 (6.6)	641 (11.3)	5,177 (91.4)
P-value	<0.001	<0.001	<0.001	<0.001	<.0001	<0.001	<0.001	<0.001
Cardiac valve surgery								
Uncontrolled	61,323 (44,151)	508 (692)	10 (8.2)	6.8 (8.8)	376.1 (168.1)	1,464 (27.0)	1,613 (29.8)	5,219 (96.3)
Controlled	45,593 (25,559)	311 (395)	6.8 (4.5)	4.0 (4.6)	342.5 (179.9)	365 (14.1)	350 (13.5)	2,426 (93.4)
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Cholecystectomy								
Uncontrolled	29,582 (27,167)	287 (387)	8.7 (8.3)	5.6 (6.9)	196.0 (431.8)	104 (17.1)	260 (42.7)	181 (29.7)
Controlled	17,180 (13,448)	203 (275)	5.0 (3.5)	3.1 (3.3)	173.7 (129.6)	71 (7.3)	207 (21.4)	79 (8.2)
P-value	<0.001	<0.001	<0.001	<0.001	0.222	<0.001	<0.001	<0.001
Cystectomy								
Uncontrolled	40,238 (62,047)	314 (372)	12 (12.6)	4.4 (5.1)	389.7 (150.2)	36 (14.3)	70 (27.8)	47 (18.7)
Controlled	29,717 (18,431)	352 (533)	9.0 (4.9)	3.0 (2.9)	484.3 (1320.8)	11 (6.4)	26 (15.2)	20 (11.7)
P-value	0.012	0.424	<0.001	0.010	0.358	0.012	0.002	0.055
Pancreatic surgery								
Uncontrolled	58,891 (49,789)	457 (618)	17 (13.2)	7.0 (9.1)	450.5 (155.0)	63 (27.2)	95 (40.9)	96 (41.4)
Controlled	37,001 (28,276)	368 (377)	10 (8.4)	3.5 (6.9)	437.2 (168.6)	16 (6.9)	57 (24.6)	31 (13.4)
P-value	<0.001	0.063	<0.001	<0.001	0.378	<0.001	<0.001	<0.001
Partial hepatic resection								
Uncontrolled	42,819 (54,515)	674 (899)	9.9 (10.4)	5.9 (8.5)	319.2 (140.4)	25 (10.7)	59 (25.3)	65 (27.9)
Controlled	21,035 (10,874)	451 (411)	5.5 (2.7)	2.1 (1.9)	294.9 (233.1)	18 (4.7)	46 (11.9)	24 (6.2)
P-value	<0.001	<0.001	<0.001	<0.001	0.107	0.004	<0.001	<0.001
Pulmonary surgery								
Uncontrolled	40,211 (33,239)	799 (1,053)	11 (9.6)	8.5 (11.6)	270.8 (118.2)	83 (27.5)	116 (38.4)	120 (39.7)
Controlled	24,361 (14,893)	347 (592)	7.1 (4.3)	3.6 (3.7)	249.3 (94.7)	57 (8.7)	106 (16.3)	122 (18.7)
P-value	<0.001	<0.001	<0.001	<0.001	0.006	<0.001	<0.001	<0.001
Radical abdominal hysterectomy								
Uncontrolled	24,203 (17,854)	592 (625)	7.1 (5.8)	5.2 (6.4)	280.4 (116.9)	4 (5.8)	26 (37.7)	10 (14.5)
Controlled	14,420 (7,444)	361 (515)	4.1 (2.5)	2.2 (2.1)	242.8 (100.2)	3 (2.4)	24 (18.9)	4 (3.1)
P-value	<0.001	0.006	<0.001	<0.001	<0.001	0.245	0.004	0.007

Abbreviations: Controlled, controlled bleeding despite hemostat use; uncontrolled, uncontrolled bleeding despite hemostat use; ICU, intensive care unit; LOS, length of stay; N, number of patients; SD, standard deviation.

Table 4 Mean adjusted all-cause costs (95% CI) and mean adjusted hospital LOS (95% CI) for controlled versus uncontrolled bleeding in patients treated with hemostatic agents, stratified by surgical procedure

Surgical category	Adjusted all-cause cost, US$ (95% CI)			Adjusted length of stay, days (95%CI)		
	Bleeding not controlled despite HA	Bleeding controlled with HA	*P*-value	Bleeding not controlled despite HA	Bleeding controlled with HA	*P*-value
Cardiac revascularization	44,198 (43,610–44,785)	35,288 (34,624–35,951)	<0.001	7.7 (7.5–7.8)	5.9 (5.8–6.1)	<0.001
Cardiac valve Surgery	60,531 (59,510–61,552)	47,245 (45,746–48,745)	<0.001	9.7 (9.5–9.9)	7.2 (7.0–7.5)	<0.001
Cholecystectomy	29,101 (27,532–30,670)	17,483 (16,248 –18,718)	<0.001	8.4 (7.9–8.9)	5.2 (4.8–5.5)	<0.001
Cystectomy	41,708 (35,541–47,876)	27,551 (19,976–35,126)	0.006	12.5 (11.2–13.7)	8.8 (7.2–10.3)	<0.001
Pancreatic surgery	58,853 (53,503–64,203)	37,039 (31,689–42,389)	<0.001	16.2 (14.7–17.7)	10.8 (9.3–12.3)	<0.001
Partial hepatic resection	43,649 (39,188–48,111)	20,535 (17,106 –23,964)	<0.001	9.8 (8.9–10.7)	5.6 (4.9–6.2)	<0.001
Pulmonary surgery	40,416 (37,886–42,946)	24,266 (22,564–25,968)	<0.001	11.3 (10.5–12.0)	7.1 (6.6–7.6)	<0.001
Radical abdominal hysterectomy	23,266 (20,458–26,075)	14,929 (12,891–16,967)	<0.001	6.8 (5.8–7.7)	4.3 (3.6–5.0)	<0.001

Note: Values presented as mean (95% CI).
Abbreviations: CI, confidence interval; LOS, length of stay; HA, hemostatic agent.

alleviate this burden. The EVARREST® fibrin sealant patch is one novel bioabsorbable combination product composed of human fibrinogen and thrombin along with a flexible composite patch that provides mechanical integrity and supports clot formation.[35] EVARREST® is supported by several clinical studies across challenging bleeding populations demonstrating rapid onset of action with high hemostasis efficacy.[27,36] A recent economic evaluation also showed that this new fibrin sealant patch was predicted to be cost saving in problematic surgical bleeding for hospital stakeholders due to hospital resources averted, such as transfusions and bleeding retreatment, versus standard of care.[37] Such results are particularly relevant in light of the findings of the current study showing significantly greater hemostat costs in uncontrolled bleeding cohorts. Several additional new hemostatic agents have also been developed that are currently undergoing clinical trials. Examples of these products include Veriset™ hemostatic patch (Covidien Inc., Mansfield, MA, USA), Fibrocaps™ (ProFibrix, Leiden, the Netherlands), and Hemopatch Sealing Hemostat (Baxter International, Deerfield, IL, USA). These products have numerous ongoing trials for the treatment of surgical bleeding across a wide range of surgery types with demonstrated effectiveness in some trials.[38–41] No economic evaluations have been published to date with these products.

Limitations

This study is not without limitations. First, it was retrospective; therefore, it was not possible to control for all potential confounding variables as can be done within a randomized controlled trial. Second, limitations of this study include those common to all claims-based studies. Specifically, the data for this study were derived from hospital discharge records designed to be used for billing rather than research. There is some degree of miscoding that is common in these records, and the records were not independently validated. Furthermore, data such as these miss clinical details that ideally would be used to further explain study results. For example, there are no disease-specific measures of severity, no clinical assessments of preoperative risk (eg, hematocrit levels), and no data on surgeon's skill level and techniques used. This information could not be captured and could not be evaluated or controlled for, as this was a retrospective database analysis. However, the potential impact of several patient and hospital characteristics was controlled for in adjusted multivariate analyses for the all-cause hospital costs as well as length of hospital stay, with adjustment having little impact on overall conclusions. Third, data are limited to the index hospitalization, so pre-existing comorbidities are not well captured. Fourth, data were only collected on hemostat class (eg, active, fibrin sealant, mechanical), and therefore it was not possible to conduct analyses on the association between specific hemostat products and bleeding control. Such information would have been useful for assessing the extent to which multiple product use or more expensive products contributed to the significantly higher total hemostat cost per patient in the uncontrolled bleeding cohort.

Conclusion

Despite the use of hemostatic agents, uncontrolled bleeding is common and is associated with significantly higher costs; longer hospitalization; and higher rates of reoperation and mortality in multiple major surgical procedures compared to controlled bleeding. There is an unmet need for newer hemostats that can improve clinical outcomes in surgery and minimize the economic burden to hospitals and payers. Future studies need to assess the clinical and economic impact of newer, highly efficacious hemostats in real-world, difficult-to-control bleeding populations.

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Author contributions

MC was involved in the study protocol design and development, data acquisition, and critical review of the manuscript. NF and SH were involved in data analysis/interpretation and development of the manuscript draft. MSB was involved in study protocol design and development, data analysis/interpretation, and critical review of the manuscript. EC was involved in study protocol design and development, data analysis/interpretation, and critical review of the manuscript. All authors have given final approval for the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Selected primary surgical procedures

ICD-9-CM procedure code	Description
Cardiac revascularization surgery	
36.03	Open chest coronary artery angioplasty
36.1x	Bypass anastomosis for heart revascularization
36.2	Heart revascularization by arterial implant
36.32	Other transmyocardial revascularization
36.39	Other heart revascularization
Cardiac valve surgery	
35.1x	Open heart valvuloplasty without replacement
35.2x	Replacement of heart valve
35.3x	Operations on structures adjacent to heart valves
35.99	Other operations on valves of heart
Cholecystectomy	
51.21	Other partial cholecystectomy (revision of prior cholecystectomy)
51.22	Cholecystectomy (open)
Cystectomy	
57.71	Radical cystectomy
57.79	Other total cystectomy
Pancreatic surgery	
52.51	Proximal pancreatectomy
52.52	Distal pancreatectomy
52.53	Radical subtotal pancreatectomy
52.59	Other partial pancreatectomy
52.6	Total pancreatectomy
52.7	Radical pancreaticoduodenectomy (Whipple procedure)
Partial hepatic resection	
50.22	Partial hepatectomy (wedge resection of liver)
50.3	Lobectomy of liver
Pulmonary surgery	
32.39	Other and unspecified segmental resection of lung
32.49	Other lobectomy of lung
32.59	Other and unspecified pneumonectomy
Radical abdominal hysterectomy	
68.69	Other and unspecified radical abdominal hysterectomy

Table S2 Hemostatic agents

Category	Products
Mechanical	Gelfoam®, Gelfoam Plus® , Surgifoam®, Avitene™ sheets, Avitene Ultrafoam™ collagen sponges, HELISTAT® & HELITENE®, INSTAT® MCH, Surgicel®, Surgicel Fibrillar™, Surgicel Nu-Knit®, Arista®AH, Hemostase MPH®, Vitasure™
Active	Thrombin-JMI®, Evithrom®, Recothrom®
Flowable	Floseal®, Surgiflo®
Fibrin sealant	Evicel®, Beriplast®, TachoSil®, Tisseel™, Artiss, Vitagel™, Vivostat®

Table S3 Major bleeding events

ICD-9-CM diagnosis or procedure code	Description
Diagnosis of bleeding	
998.11	Hemorrhage complicating a procedure
998.12	Hematoma complicating a procedure
Procedures to control bleeding	
34.09	Other incision of pleura, including creation of pleural window for drainage, intercostal stab, open chest drainage
39.98	Control of hemorrhage not otherwise specified
44.44	Transcatheter embolization for gastric or duodenal bleeding
44.49	Other control of hemorrhage of stomach or duodenum – that with gastronomy
54.19	Other laparotomy: drainage of intraperitoneal abscess or hematoma
39.41	Control of hemorrhage following vascular surgery
34.03	Reopening of recent thoracotomy site
54.12	Reopening of recent laparotomy site for: control of hemorrhage, exploration, incision of hematoma
57.93	Control of (postoperative) hemorrhage of bladder
Charges billed for	Hemovac drainage devices
Erythropoietin	
Charges billed for	Epogen, Procrit, Aranesp, Darbepoetin
Blood products	
99.00	Perioperative autologous transfusion of whole blood or blood components
99.02	Transfusion of previously collected autologous blood
99.03	Other transfusion of whole blood
99.04	Transfusion of packed cells
99.05	Transfusion of platelets
99.07	Transfusion of other serum
99.08	Transfusion of blood expander
99.09	Transfusion of other substance
Charges billed for	Cryoprecipitates, fresh frozen plasma, red blood cells, plasma, platelets, whole blood

Table S4 Infections

ICD-9-CM diagnosis code	Description
Postoperative infections	
998.5x	Postoperative infection
996.6x	Infection and inflammatory reaction due to internal prosthetic device, implant, and graft
Infection due to medical care	
999.3x	Other infection: infection due to central venous catheter; infection following other infusion, injection, transfusion, or vaccination
Septicemia	
038.x	Septicemia
785.52	Septic shock
995.91	Sepsis
995.92	Severe sepsis
998.0	Postoperative shock
Other bacterial infections	
040.0	Gas gangrene
040.8x	Other specified bacterial diseases
041.x	Bacterial infection in conditions classified elsewhere and of unspecified site
790.7	Bacteremia
Skin infections	
682.x	Other cellulitis and abscess
686.x	Other local infections of skin and subcutaneous tissue
Urinary tract infections	
112.2	Candidiasis of other urogenital sites
590.1	Acute pyelonephritis
590.3	Pyeloureteritis cystica
590.8x	Other pyelonephritis or pyonephrosis, not specified as acute or chronic
590.9	Infection of kidney, unspecified
595.0	Acute cystitis
595.3	Trigonitis
599.0	Urinary tract infection, site not specified
996.64	Infection due to indwelling urinary catheter
Pneumonia	
039.1	Pulmonary actinomycotic infections
112.4	Candidiasis of lung
117.9	Other and unspecified mycoses
136.3	Pneumocystosis
466.19	Acute bronchiolitis due to other infectious organisms
480.x	Viral pneumonia
481	Pneumococcal pneumonia (*Streptococcus pneumoniae* pneumonia)
482.x	Other bacterial pneumonia
483.x	Pneumonia due to other specified organism
484.x	Pneumonia in infectious diseases classified elsewhere
485	Bronchopneumonia, organism unspecified
486	Pneumonia, organism unspecified
487.0	With pneumonia
507.x	Pneumonitis due to solids and liquids
513.0	Abscess of lung
516.8	Other specified alveolar and parietoalveolar pneumonopathies
997.3x	Respiratory complications
Gynecological infections	
614.0	Acute salpingitis and oophoritis
614.2	Salpingitis and oophoritis not specified as acute, subacute, or chronic
614.3	Acute parametritis and pelvic cellulitis
614.4	Chronic or unspecified parametritis and pelvic cellulitis
614.5	Acute or unspecified pelvic peritonitis, female
614.6	Pelvic peritoneal adhesions, female (postoperative) (postinfection)
614.8	Other specified inflammatory disease of female pelvic organs and tissues
614.9	Unspecified inflammatory disease of female pelvic organs and tissues
615.0	Acute inflammatory diseases of uterus, except cervix
615.9	Unspecified inflammatory disease of uterus
670.0x	Major puerperal infection
672.0x	Pyrexia of unknown origin during the puerperium
Septic embolism	
673.3x	Obstetrical pyemic and septic embolism
Fever	
780.6x	Fever and other physiologic disturbances of temperature regulation

(*Continued*)

(*Continued*)

Table S5 Transfusion coding descriptions

ICD-9-CM procedure or standard charge code	Description
Transfusion of platelets	
99.05	Transfusion of platelets
Transfusion of coagulation factors	
99.06	Transfusion of coagulation factors
Other transfusion	
99.00	Perioperative autologous transfusion of whole blood or blood components
99.01	Autologous whole blood transfusion
99.02	Transfusion of previously collected autologous blood
99.03	Other transfusion of whole blood
99.04	Transfusion of packed cells
99.07	Transfusion of other serum
99.08	Transfusion of blood expander
99.09	Transfusion of other substance
V58.2	Blood transfusion, no diagnosis
380381000010000	Red Cells Packed 1 Unit
380381000010007	Red Cells Packed 7 Units
380381000010008	Red Cells Packed 8 Units
380381000010009	Red Cells Packed 9 Units
380381000010010	Red Cells Packed 10 Units
380381000020000	Red Cells Packed 2 Units
380381000030000	Red Cells Packed 3 Units
380381000040000	Red Cells Packed 4 Units
380381000050000	Red Cells Packed 5 Units
380381000060000	Red Cells Packed 6 Units
380381000210000	Red Cells Autologous 1 Unit
380381000210005	Red Cells Autologous 5 Units
380381000210006	Red Cells Autologous 6 Units
380381000210007	Red Cells Autologous 7 Units
380381000210008	Red Cells Autologous 8 Units
380381000210009	Red Cells Autologous 9 Units
380381000210010	Red Cells Autologous 10 Units
380381000220000	Red Cells Autologous 2 Units
380381000230000	Red Cells Autologous 3 Units
380381000240000	Red Cells Autologous 4 Units
380381000310000	Red Cells Leukocyte Poor 1 Unit
380381000310005	Red Cells Leukocyte Poor 5 Units
380381000310006	Red Cells Leukocyte Poor 6 Units
380381000310007	Red Cells Leukocyte Poor 7 Units
380381000310008	Red Cells Leukocyte Poor 8 Units
380381000310009	Red Cells Leukocyte Poor 9 Units
380381000310010	Red Cells Leukocyte Poor 10 Units
380381000320000	Red Cells Leukocyte Poor 2 Units
380381000330000	Red Cells Leukocyte Poor 3 Units
380381000340000	Red Cells Leukocyte Poor 4 Units
380381000410000	Red Cells Washed 1 Unit
380381000410003	Red Cells Washed 3 Units
380381000410004	Red Cells Washed 4 Units
380381000410005	Red Cells Washed 5 Units
380381000410006	Red Cells Washed 6 Units
380381000410007	Red Cells Washed 7 Units
380381000410008	Red Cells Washed 8 Units
380381000410009	Red Cells Washed 9 Units
380381000410010	Red Cells Washed 10 Units
380381000420000	Red Cells Washed 2 Units
380381000510000	Red Cells Deglycerolized 1 Unit
380381000510003	Red Cells Deglycerolized 3 Units
380381000510004	Red Cells Deglycerolized 4 Units
380381000510005	Red Cells Deglycerolized 5 Units
380381000510006	Red Cells Deglycerolized 6 Units
380381000510007	Red Cells Deglycerolized 7 Units
380381000510008	Red Cells Deglycerolized 8 Units
380381000510009	Red Cells Deglycerolized 9 Units
380381000510010	Red Cells Deglycerolized 10 Units
380381000520000	Red Cells Deglycerolized 2 Units
380381000610000	Red Cells Directed 1 Unit
380381000610002	Red Cells Directed 2 Units
380381000610003	Red Cells Directed 3 Units
380381000610004	Red Cells Directed 4 Units
380381000610005	Red Cells Directed 5 Units
380381000610006	Red Cells Directed 6 Units
380381000610007	Red Cells Directed 7 Units
380381000610008	Red Cells Directed 8 Units
380381000610009	Red Cells Directed 9 Units
380381000610010	Red Cells Directed 10 Units
380382000010000	Whole Blood 1 Unit
380382000010002	Whole Blood 2 Units
380382000010003	Whole Blood 3 Units
380382000010004	Whole Blood 4 Units
380382000010005	Whole Blood 5 Units
380382000010006	Whole Blood 6 Units
380382000010007	Whole Blood 7 Units
380382000010008	Whole Blood 8 Units
380382000010009	Whole Blood 9 Units
380382000010010	Whole Blood 10 Units
380382000210000	Whole Blood Autologous 1 Unit
380382000210005	Whole Blood Autologous 5 Units
380382000210006	Whole Blood Autologous 6 Units
380382000210007	Whole Blood Autologous 7 Units
380382000210008	Whole Blood Autologous 8 Units
380382000210009	Whole Blood Autologous 9 Units
380382000210010	Whole Blood Autologous 10 Units
380382000220000	Whole Blood Autologous 2 Units
380382000230000	Whole Blood Autologous 3 Units
380382000240000	Whole Blood Autologous 4 Units
380382000310000	Whole Blood Irradiated 1 Unit
380382000310002	Whole Blood Irradiated 2 Units
380382000310003	Whole Blood Irradiated 3 Units
380382000310004	Whole Blood Irradiated 4 Units
380382000310005	Whole Blood Irradiated 5 Units
380382000310006	Whole Blood Irradiated 6 Units
380382000310007	Whole Blood Irradiated 7 Units
380382000310008	Whole Blood Irradiated 8 Units
380382000310009	Whole Blood Irradiated 9 Units
380382000310010	Whole Blood Irradiated 10 Units

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