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Multistate modelling to estimate excess length of stay and risk of death associated with organ/space infection after elective colorectal surgery

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SUMMARY

Background: Accounting for time-dependency and competing events are strongly recommended to estimate excess length of stay (LOS) and risk of death associated with healthcare-associated infections.

Aim: To assess the effect of organ/space (OS) surgical site infection (SSI) on excess LOS and in-hospital mortality in patients undergoing elective colorectal surgery (ECS).

Methods: A multicentre prospective adult cohort undergoing ECS, January 2012 to December 2014, at 10 Spanish hospitals was used. SSI was considered the time-varying exposure and defined as incisional (superficial and deep) or OS. Discharge alive and death were the study endpoints. The mean excess LOS was estimated using a multistate

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model which provided a weighted average based on the states patients passed through. Multivariate Cox regression models were used to assess the effect of OS-SSI on risk of discharge alive or in-hospital mortality.

Findings: Of 2778 patients, 343 (12.3%) developed SSI: 194 (7%) OS-SSI and 149 (5.3%) incisional SSI. Compared to incisional SSI or no infection, OS-SSI prolonged LOS by 4.2 days (95% confidence interval (CI): 4.1—4.3) and 9 days (8.9—9.1), respectively, reduced the risk of discharge alive (adjusted hazard ratio (aHR): 0.36 (95% CI: 0.28—0.47) and aHR: 0.17 (0.14—0.21), respectively), and increased the risk of in-hospital mortality (aHR: 8.02 (1.03—62.9) and aHR: 10.7 (3.7—30.9), respectively).

Conclusion: OS-SSI substantially extended LOS and increased risk of death in patients undergoing ECS. These results reinforce OS-SSI as the SSI with the highest health burden in ECS.

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Introduction

Surgical site infections (SSIs) are one of the most severe and dreaded healthcare-associated infections (HCAIs) in elective colorectal surgery (ECS). These infections increase morbidity and mortality, and prolong length of stay (LOS), thereby increasing patient and health costs [1,2]. Among SSIs, organ/space (OS)-SSI has been associated with the worst outcomes [3—5].

Since colorectal surgery is a cornerstone of treatment for colorectal cancer — the third most common cancer diagnosed in developed countries — avoiding these HCAIs is an urgent matter. Multiple strategies have been shown to be successful in preventing SSIs; however, recent studies still show high rates of OS-SSI associated with colorectal surgery [6—13].

Measuring the health cost of OS-SSI accurately can facilitate joint efforts by all stakeholders to implement targeted prevention strategies. Currently, from the hospital perspective, the cost of HCAIs is mostly due to extending patient LOS, which determines missed new hospital admissions [14,15]. When estimating LOS due to HCAIs, applying statistical models that consider the time-dependent nature of the infection has been recommended. This approach permits a better control of time-dependent bias and avoids overestimation of excess LOS [16,17].

To date, studies reporting the effect of SSI on LOS in colorectal surgery have not considered time-dependent bias [1,4,12]. The purpose of the present study is therefore to assess the health costs of OS-SSI measured in terms of excess LOS and risk of death during the hospital stay in a prospective cohort of patients undergoing ECS, taking into account timing of infection and competing events.

Methods

Setting and study design

This was a multicentre prospective cohort study of adult (aged $\geq$18 years) patients who underwent ECS from January 2012 to December 2014, at 10 hospitals in Catalonia, Spain. The hospital characteristics are shown in Table I. All these hospitals routinely report data to the regional surveillance programme for HCAIs: VINCat [5,18]. All patients hospitalized for ECS at the different hospitals were followed up until discharge or death. Patients with pre-existing infection at the time of surgery or with SSIs diagnosed after discharge were excluded.

Outcomes

The main outcomes were excess LOS and in-hospital mortality of patients who acquired an OS-SSI during their stay for ECS. Risk factors associated with the longest excess LOS due to OS-SSI defined as excess LOS >75th percentile (p75) were also assessed.

Table I

Characteristics of acute hospitals participating in the study, 2012—2014

Hospital	Type	Acute beds	Admissions	ECS	Bed-days[a]
1	University hospital	760	87,899	449	4430
2	University hospital	518	50,004	454	3347
3	Medium-sized teaching hospital	295	36,123	214	1742
4	Medium-sized teaching hospital	431	58,945	408	2904
5	Community hospital	121	17,077	220	1407
6	Medium-sized teaching hospital	200	23,796	159	1419
7	University hospital	450	46,495	233	2040
8	Medium-sized teaching hospital	283	39,037	295	2217
9	Community hospital	130	38,332	127	965
10	Medium-sized teaching hospital	276	28,177	219	1340
Total		3464	425,885	2778	21,811

ECS, elective colorectal surgery.

[a] Bed-days related to patients undergoing elective colorectal surgery in each hospital.

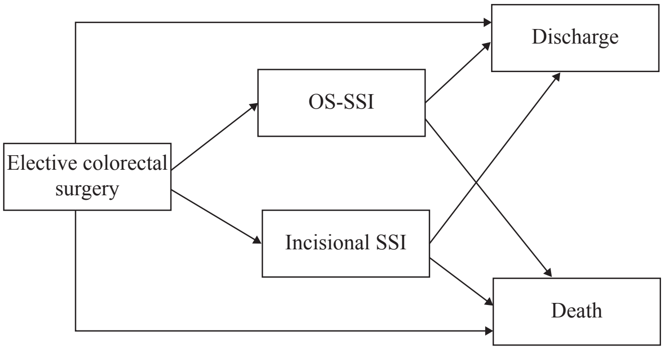

Figure 1. Multistate model adopted for the analysis of excess length of stay of patients with surgical site infection. Patients discharged without infection underwent post-discharge surveillance for up to 30 days after surgery. In all, 115 patients developed an SSI after discharge (71 incisional SSIs and 44 organ/space (OS)-SSIs). Of the patients who developed SSIs, 18 patients with incisional SSI and 40 with OS-SSI required readmission (these patients were not included in the analysis).

Independent variables

Age, sex, American Society of Anesthesiologists' (ASA) physical status, type of procedure (colon/rectal), laparoscopic approach, adequacy of intravenous antibiotic prophylaxis (IAP), and primary diagnosis (cancer, inflammatory bowel disease (IBD) or other) were considered as potential baseline confounders [19]. Age (<65 and ≥65 years) and ASA (I—II and III—IV) were dichotomized for the analysis.

Definitions

SSIs were defined according to the Centers for Disease Control and Prevention criteria and divided, for the purpose of this study, into incisional (superficial or deep) and OS infection [20].

Adequate antibiotic prophylaxis was considered when the following three conditions were met: antibiotics administered according to the local evidence-based protocol at each hospital, completion of the infusion within 60 min before the surgical incision, and perioperative antibiotic redosing if indicated.

Data collection

Data were obtained from the VINCat database, based on standardized protocols, which prospectively collects information related to demographics, comorbidities, perioperative characteristics, and 30-day postoperative outcomes for eligible surgical procedures [18,21].

Statistical analysis

Incidence densities in the cohort were calculated by dividing the number of events by the number of patient-days at risk per 1000. To estimate excess LOS, we used a multistate modelling as outlined by Beyersmann *et al.* [22]. Patients entered the initial state after the ECS and exited by entering one of the two competing states: death or discharge alive, with or without acquiring an SSI, which was the time-dependent exposure of interest. This approach allowed us to estimate the mean excess LOS of patients with SSI (OS-SSI or incisional SSI) with respect to uninfected patients. The multistate model provides a weighted average of the LOS based on the path followed by patients (Figure 1). Patients who were still in hospital 30 days after surgery were artificially right-censored to avoid the influence of outliers on LOS.

Proportional hazards models were established for the time to mortality during admission and the time to discharge alive, with a set of risk factors including the SSI indicators. The results are shown as hazard ratio (HR) and the corresponding confidence intervals for the univariate and multivariate models. HRs were obtained from the cause-specific hazard models for mortality or for discharge alive. In each model, 'hospital' was introduced as strata variable to take into account potential differences in death or discharge alive between hospitals.

To characterize patients with the longest excess LOS, a binary indicator of excess LOS $>$p75 ($>$16 days) was computed. Thus, $Y = 1$ was assigned for values with the highest excess LOS ($>$p75), and $Y = 0$ was assigned otherwise. We established a generalized linear model for the response variable Y with demographic and clinical characteristics as covariates. The sample size used for this model was 2629, since patients with incisional SSI were excluded. The results are shown as odds ratios (ORs) and the corresponding confidence intervals (CIs) for the univariate and multivariate models.

Multivariate models included covariates of the univariate models with $P < 0.10$ and relevant variables from a clinical point of view.

All the results were obtained with SAS v9.4, SAS Institute, Inc. (Cary, NC, USA) and R v3.4.4 (etm package).

Ethics

This study was approved by the Ethics Committee of Hospital Universitari de Bellvitge (reference: PR092/16).

Results

A total of 2778 patients were included in the cohort; cancer was the main cause of surgery 2623 (94%). During the hospital stay, 343 patients (12.3%) developed SSI. Of those, 194 (7%) had OS-SSI and 149 (5.3%) incisional SSI. The incidence density of overall SSI was 15.7 per 1000 patient-days at risk; 8.9 and 6.8 per 1000 patient-days at risk for OS-SSI and incisional SSI, respectively. Infection occurred in a median time of six days after surgery for both OS-SSI and incisional SSI. The median LOS for patients without infection was six days (interquartile range: 5—9); and 24 days (18—36) and 15 days (10—22) for patients with OS-SSI and incisional SSI, respectively. Baseline patient characteristics are shown in Table II.

Excess of length of stay

At the end of the study, 2649 patients (95.4%) were discharged, 22 died (0.8%), and 107 (3.8%) remained in hospital. Compared to patients who did not develop an infection or who had an incisional SSI, OS-SSI increased LOS an average of 9 days (95% CI: 8.9—9.1) and 4.2 days (4.1—4.3), respectively. The risk of discharge alive decreased in patients with OS-SSI (aHR: 0.17;

Table II
Baseline, perioperative characteristics, and crude length of stay and mortality rates of patients in the cohort

Variable	Non-SSI	Incisional SSI	OS-SSI
	($N = 2\ 435$)	($N = 149$)	($N = 194$)
Sex, male	1469 (60.3%)	106 (71.1%)	149 (76.8%)
Age (years), median (IQR)	64.5 (60.7–77.7)	70.9 (62.2–79.1)	70.3 (61.1–78.7)
ASA class $\geq$III	958 (39.3%)	79 (53.0%)	91 (46.9%)
Primary diagnosis			
Cancer	2303 (94.6%)	142 (95.3%)	178 (91.7%)
Inflammatory bowel disease	58 (2.4%)	4 (2.6%)	8 (4.1%)
Other	74 (3.0%)	3 (2.0%)	8 (4.1%)
Type of procedure			
Colon	1675 (68.8%)	88 (59.1%)	116 (59.8%)
Rectal	760 (31.2%)	61 (40.9%)	78 (40.2%)
Laparoscopic approach	1634 (67.1%)	77 (51.7%)	101 (52.0%)
Adequate intravenous prophylaxis	1983 (81.4%)	121 (81.2%)	156 (80.4%)
Operating time >75th percentile[a]	979 (40.2%)	58 (38.9%)	87 (44.8%)
NNIS risk index $\geq$1	796 (32.7%)	73 (48.9%)	88 (45.4%)
Length of stay (days), median (IQR)	6 (5–9)	15 (10–22)	24 (18–36)
Days from surgery to infection, median (IQR)		6 (5–10)	6 (4–9)
Days from infection to discharge, median (IQR)		8 (4–13)	18 (11–28)
In-hospital mortality	5 (0.2%)	1 (0.7%)	16 (8.2%)

SSI, surgical site infection; OS, organ/space; IQR, interquartile range; ASA, American Society of Anesthesiologists' physical status; IBD, inflammatory bowel disease; NNIS, National Nosocomial Infections Surveillance.

[a] Duration of operative procedure >180 min.

95% CI: 0.14–0.21) and with incisional SSI (aHR: 0.46; 0.39–0.55), although the greatest effect was associated with OS-SSI (Table III).

Risk factors associated with the longest excess LOS due to OS-SSI were receiving inadequate IAP (aOR: 1.10; 95% CI: 1.01–1.20; $P = 0.03$) and non-laparoscopic approach (1.06; 0.99–1.15; $P = 0.08$) (Table IV).

In-hospital mortality

Of the 22 patients who died during their hospital stay, five were uninfected, one had incisional SSI, and 16 had OS-SSI. After accounting for demographics and perioperative characteristics, patients with OS-SSI had a higher risk of death than patients with incisional SSI (aHR: 8.02; 95% CI: 1.03–62.9) or without infection (10.7; 3.7–30.9) (Table III).

Discussion

This study shows that, among SSIs, OS-SSI had the greatest burden on LOS and mortality in patients undergoing ECS in a large cohort of patients. The results are consistent with those reported in the literature; however, previous studies frequently used matching designs to estimate excess LOS, a type of design that overestimates LOS, since they do not consider time-dependency of the infection [1,4,23–26].

Excess LOS attributed to SSI varies from 4.1 to 15 days, although most studies reporting these data include a small number of surgeries and evaluate data on patients undergoing different types of surgical procedure [1,4,23]. Our study is the first using multistate modelling to estimate excess LOS in ECS. Patients with OS-SSI stayed an average of nine additional days in hospital, a period greater than the median stay of patients without infection in the cohort. Since ECS is currently a high-volume procedure worldwide due to the incidence of cancer, improving efforts to avoid this preventable complication would free up hospital capacity to treat additional patients [27].

There is a paucity of studies exploring factors that predispose to a prolonged stay in colorectal surgery. In such studies, age, comorbidities, open surgery approach, prolonged ileus, or infection are associated with the longest hospital stays [28–30]. Our results suggest that the longest admissions occurred in patients receiving inadequate IAP or undergoing an open surgery. In contrast, no associations with age, the highest ASA score, type of procedure or primary diagnosis were observed. Since adequate IAP and laparoscopic access to the abdominal cavity prevent postoperative complications, these factors may act as surrogate marker for confounders that could influence LOS, such as prolonged ileus. Unfortunately, a lack of data prevented us exploring this subject further [31,32].

ECS is considered a safe procedure since it is associated with low mortality rates, ranging from 0.9% to 4% [33,34]. In our study, the mortality rate was <1% in patients with incisional SSI or those who did not have an infection; but for patients with OS-SSI, the risk of death during admission was 10 times higher than the risk for uninfected patients. Interestingly, a recent study conducted in the UK found that, among postoperative infections in ECS, OS-SSI was the only infection associated with an increase in one-year mortality [35].

The strength of the present study is that we have considered the time-dependent nature of SSI and competing risk events, to obtain a more precise estimation of extra LOS and risk of mortality in a large prospective cohort of patients. Notably, the analysis enables us to show that incisional SSI has a slight effect on LOS and no effect on mortality. This reinforces the idea that OS-SSI in ECS is the SSI carrying the greatest health burden.

Table III

Estimated excess length of stay (LOS) and hazards models for discharge or death

Comparison	Excess LOS (days), mean (95% CI)	Hazard ratio of discharge alive		Hazard ratio of death[a]	
		Model 1 HR (95% CI)	Model 2 aHR (95% CI)	Model 1 HR (95% CI)	Model 2 aHR (95% CI)
Incisional SSI vs uninfected	2.9 (2.8—3.0)	0.45 (0.38—0.53)	0.46 (0.39—0.55)	—[b]	—[b]
OS-SSI vs uninfected	9 (8.9—9.1)	0.18 (0.15—0.22)	0.17 (0.14—0.21)	8.14 (2.73—24.23)	10.77 (3.75—30.89)
OS-SSI vs incisional SSI	4.2 (4.1—4.3)	0.38 (0.29—0.49)	0.36 (0.28—0.47)	6.69 (0.86—52.14)	8.02 (1.03—62.89)

aHR, adjusted hazard ratio; CI, confidence interval; SSI, surgical site infection; OS, organ/space.

Model 1: univariate analysis. Model 2: Model 1 adjusted for age, sex, American Society of Anesthesiologists' physical status, type of procedure, laparoscopic approach, and adequate intravenous antibiotic prophylaxis.

[a] Includes mortality during the hospital stay.

[b] As only one patient died during the stay, in the incisional SSI group the hazard for mortality has not been calculated.

Table IV

Univariate and multivariate analysis of risk factors for the longest length of stay due to OS-SSI

Risk factor	OR (95% CI)	aOR (95% CI)	*P*-value
Age ≥65 years	1 (0.94—1.07)	1 (0.94—1.07)	0.96
Male sex	0.95 (0.90—1.02)	0.95 (0.89—1.02)	0.15
ASA class ≥III	0.99 (0.93—1.07)	1 (0.93—1.07)	0.97
Type of procedure, colon	0.99 (0.93—1.07)	0.99 (0.92—1.07)	0.87
Non-laparoscopic approach	1.06 (0.99—1.14)	1.06 (0.99—1.15)	0.08
Inadequate intravenous antibiotic prophylaxis	1.10 (1.01—1.20)	1.10 (1.01—1.20)	0.03
Primary diagnosis			
Cancer	0.91 (0.77—1.07)		
IBD	1.20 (0.93—1.56)		
Other	1.06 (0.85—1.32)		

OS-SSI, organ/space surgical site infection; OR, odds ratio; aOR, adjusted odds ratio; ASA, American Society of Anesthesiologists' physical status; IBD, inflammatory bowel disease.

Longest length of stay = excess length of stay >p75.

The analysis included 2629 patients (incisional SSIs were excluded). Of these, 895 patients had an excess length of stay >p75 (>16 days), 105 had OS-SSIs.

The major limitation of this work is that it only included infections detected during hospitalization. Since more than 20% of SSIs are detected post discharge if we included those patients in the analysis, the real effect of OS-SSIs on LOS may be miscalculated [36]. To include patients with OS-SSIs diagnosed post discharge in the analysis, two approaches could be proposed: including a new path from discharge to infection in the multistate model; or using models for multivariate survival and recurrent events. A further limitation is the unadjusted nature of the excess LOS analysis; although to overcome that, we computed a binary indicator of excess LOS and adopted a generalized linear model. However, unmeasured information on postoperative details or on time-varying covariates, such as ICU admission, might be confounding the results [37].

In summary, accounting for time-dependency and competing events, OS-SSI substantially extends LOS and increases risk of mortality. These results reinforce the notion that OS-SSI is the SSI with the highest health burden in ECS. Hence, OS-SSI prevention should be a priority for all healthcare providers.

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Conflict of interest statement

None declared.

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