Journal of Hospital Infection 147 (2024) 123–132

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Costs and resource utilization patterns in surgical site infections: a pre-COVID-19 perspective from France, Germany, Spain, and the UK

J. Salmanton-García[a,b,c], C. Bruns[a,b,c], J. Rutz[a,b], M. Albertsmeier[d], J. Ankert[e], L. Bernard[f], C. Bataille[g], E. Couvé-Deacon[g], M. Fernández-Ferrer[h,i], J. Fortún[j], A. Galar[k], E. Grill[l], T. Guimard[m], A.Y. Classen[b,c], J.J. Vehreschild[b,c], J. Stemler[a,b,c], J-H. Naendrup[b,c], J. Hampl[b,c], B. Tallon[n], R. Sprute[a,b,c], J.P. Horcajada[i,h], J. Mollar-Maseres[o], P. Muñoz[k], M.W. Pletz[e], F. Serracino-Inglott[p], A. Soriano[q], T.O. Vilz[r], H. Seifert[a,b,c], O.A. Cornely[a,b,c], S.C. Mellinghoff[a,b,c,*,†], B.J. Liss[s,t,†], S.M. Wingen-Heimann[b,u,†], on behalf of the SALT study group[‡]

[a] *Faculty of Medicine and University Hospital Cologne, Institute of Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany*
[b] *Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn–Cologne Duesseldorf (CIO ABCD) and Excellence Center for Medical Mycology, University of Cologne, Cologne, Germany*
[c] *German Centre for Infection Research (DZIF), Partner Site Bonn–Cologne, Cologne, Germany*
[d] *Department of General, Visceral and Transplantation Surgery, LMU University Hospital, Ludwig-Maximilians-Universität Munich, Munich, Germany*
[e] *Institute of Infectious Diseases and Infection Control, University Hospital Jena, Jena, Germany*
[f] *Service de Médecine Interne et Maladies Infectieuses, Centre Hospitalier Régional Universitaire de Tours, Tours, France*
[g] *INSERM, CHU Limoges, UMR 1092, Université Limoges, Limoges, France*
[h] *Hospital del Mar-IMIM, Universitat Pompeu Fabra, Barcelona, Spain*
[i] *Centro de Investigación Biomédica en Red de Enfermedades Infecciosas, Instituto de Salud Carlos III, CIBERINFEC, Madrid, Spain*
[j] *Ramón y Cajal University Hospital, CIBERINFEC, IRYCIS, Madrid, Spain*
[k] *Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain*
[l] *Institute for Medical Information Processing, Biometrics and Epidemiology, Ludwig-Maximilians-Universität München (LMU), Munich, Germany*
[m] *Service de Médecine Post-Urgence, CH Départemental de Vendée, La Roche Sur Yon, France*
[n] *Manchester Academic Health Science Centre, Manchester University NHS Foundation Trust, Manchester, UK*
[o] *Preventive Medicine Department, La Fe University and Polytechnic Hospital, Valencia, Spain*
[p] *Manchester University NHS Foundation Trust, Manchester, UK*
[q] *Hospital Clínic de Barcelona, IDIBAPS, University of Barcelona, CIBERINFEC, Barcelona, Spain*

* Corresponding author. Address: University of Cologne, Herderstraße 52–54, 50931 Cologne, Germany. Tel.: +49 221 478 85523; fax: +49 221 478 1421445.

E-mail address: sibylle.mellinghoff@uk-koeln.de (S.C. Mellinghoff).

† Shared senior authorship.

‡ SALT study group: A. Pegeot, H. Durand, A. Ménard, A. Potart, C. Porché, M.C. Hallouin-Bernard, A.V. Moreno, M. Solá, R. Onori, F. Goia, R. Escudero, H. Martínez-Morel, M. Luján, R. Pérez, A. Panes, K. Rhodes, C.E.M. Koll, F.C. Koehler, F.B. Cornely, S. Budin.

https://doi.org/10.1016/j.jhin.2024.02.019

[r] Klinik und Poliklinik für Allgemein-, Viszeral-, Thorax- und Gefäßchirurgie, Universitätsklinikum Bonn, Venusberg Campus 1, Bonn, Germany
[s] Department I of Internal Medicine, Helios University Hospital Wuppertal, Wuppertal, Germany
[t] School of Medi-Cine, Faculty of Health, Witten/Herdecke University, Witten, Germany
[u] FOM University of Applied Sciences, Essen, Germany

A R T I C L E I N F O

Article history:
Received 15 December 2023
Accepted 6 February 2024
Available online 11 March 2024

Keywords:
Surgical site infection
Staphylococcus aureus
Hospital-acquired infection

S U M M A R Y

Background: Surgical site infections (SSIs), mainly caused by *Staphylococcus aureus*, pose a significant economic burden in Europe, leading to increased hospitalization duration, mortality, and treatment costs, particularly with drug-resistant strains such as meticillin-resistant *S. aureus*.
Aim: To conduct a case–control study on the economic impact of *S. aureus* SSI in adult surgical patients across high-volume centres in France, Germany, Spain, and the UK, aiming to assess the overall and procedure-specific burden across Europe.
Methods: The SALT study is a multinational, retrospective cohort study with a nested case–control analysis focused on *S. aureus* SSI in Europe. The study included participants from France, Germany, Italy, Spain, and the UK who underwent invasive surgery in 2016 and employed a micro-costing approach to evaluate health economic factors, matching *S. aureus* SSI cases with controls.
Findings: In 2016, among 178,904 surgical patients in five European countries, 764 developed *S. aureus* SSI. Matching 744 cases to controls, the study revealed that *S. aureus* SSI cases incurred higher immediate hospitalization costs (€8,810), compared to controls (€6,032). Additionally, *S. aureus* SSI cases exhibited increased costs for readmissions within the first year post surgery (€7,961.6 versus €5,298.6), with significant differences observed. Factors associated with increased surgery-related costs included the cost of hospitalization immediately after surgery, first intensive care unit (ICU) admission within 12 months, and hospital readmission within 12 months, as identified through multivariable analysis.
Conclusion: The higher rates of hospitalization, ICU admissions, and readmissions among *S. aureus* SSI cases highlight the severity of these infections and their impact on healthcare costs, emphasizing the potential benefits of evidence-based infection control measures and improved patient care to mitigate the economic burden.

Introduction

Surgical site infections (SSIs) are among the most common hospital-acquired infections (HAIs) and constitute an important quality criterion in health research [1]. The majority of SSIs in Europe are caused by *Staphylococcus aureus* (SA) [2]. Treatment of SA-SSI is challenging, especially in the context of drug- or multidrug-resistant pathogens such as meticillin-resistant SA (MRSA), while SSIs increase duration of hospitalization, death rates and treatment costs [3,4].

Treatment costs depend, among other factors, on the depth of SSI (superficial, deep, or organ space) and the procedure performed. However, the exact treatment costs vary widely, as previous estimates are based on limited data from single centres, provider networks, or highly aggregated data from surveillance programmes, with estimated average costs between €1,000 and €20,000 per SA-SSI case [5–9]. Consequently, assessment of costs for inpatient treatment of SA-SSI on a large scale has been difficult, as different perspectives were used for the current evidence of SA-SSI-related costs [10].

Here, we performed a health economic case–control study nested within a cohort of adult surgical patients in selected high-volume centres in France, Germany, Spain, and the UK. Cases were documented manually and thereby provide not only epidemiological, but also health economic data of resource utilization. The primary objective of this sub-study was to determine the overall and procedure-specific health economic burden of SA-SSI across Europe.

Methods

SALT study

The SALT study (Epidemiology of SA-SSI in Europe) is a multinational, multicentre, retrospective cohort study with nested case–control analysis [11,12]. The study sought advice from the Research Ethics Commission of the University of Cologne (No. 17-078) and obtained a waiver for informed consent due to the retrospective nature and anonymous data capture strategy. The study was registered on clinicaltrials.gov under NCT03353532. Data collection was performed by using an online eCRF accessible via www.clinicalsurveys.net, an established platform for epidemiological and health economic studies (EFS Summer 2021, TIVIAN, Cologne, Germany) [13–17]. Further information of the SALT study can be found elsewhere [12].

Inclusion criteria

To be included in the study, participants had to undergo invasive surgery in 2016 and be aged $\geq$18 years at the time of surgery. Minimally invasive biopsies, eye surgery, patients with SSI at the time of surgery, and cases with missing data defined as 'missing completely at random' were excluded. The study evaluated data at two levels: the overall cohort and the case–control population. Infectious disease specialists reviewed all anonymized data and cases. SA-SSI cases were identified by cross-matching laboratory data of all SA isolates with patients who underwent surgery, resulting in a comprehensive list of possible SA-SSI cases. To confirm SA-SSI, non-SA-SSI isolates (e.g. contamination, colonization, etc.) were excluded. Each identified possible case underwent manual review. True cases were defined as having either a documented diagnosis of SSI or showing both clinical symptoms suspicious for SSI and receiving an intervention. SA identification in the absence of these conditions was considered as contamination or colonization and not eligible for the study. SSI cases caused by pathogens other than SA and culture-negative SSI were also excluded. A committee of infectious disease specialists and surgeons at the coordinating centre defined codes not involving surgical procedures. Minimally invasive procedures and eye surgery, which were excluded from the study, were listed in the appendix. Country-specific procedure codes were harmonized [11].

Health economic evaluation

The health economic evaluation was conducted in line with the Consolidated Health Economic Evaluation Reporting Standards 2022 [18]. The following single-cost factors were included for a micro-costing approach as recommended by national and international recommendations: treatment on different hospital wards (general ward, intermediate care unit, intensive care unit (ICU)), diagnostic and laboratory procedures, and invasive mechanical ventilation [19,20]. For all cost factors, personnel and material costs were considered. Resource costs of drug administration were not calculated. Double counting of costs was avoided by a stringent consideration of daily costs of each observed patient. To assess outcomes and resource costs, SA-SSI cases were matched with controls who underwent the same procedure using optimal propensity score matching based on cohort data (age, diabetes, procedure duration percentile for that procedure, and sex). Controls were verified to be SSI-free before inclusion. Controls who were later found to have had an SSI were excluded, and new cases were matched. All costs are presented in euros, year 2016 values, and the hospital perspective was used. Pounds sterling were converted into euros by using the exchange rate by the European Central Bank (ECB) on January 1st, 2016. Due to an observational timeframe of $\leq$12 months, no sensitivity analysis regarding annual discount rates or inflation was performed. For robust results and comparison of international healthcare values, an established methodology developed by the Organization for Economic Cooperation and Development (OECD) was used [21,22]. This methodology was also used in a recently published pan-European cost and resource utilization study of *Clostridioides difficile* infections, another frequent nosocomial infection across Europe [23].

Statistical analysis

Statistical comparisons were conducted to assess differences between SA-SSI cases and controls in terms of demographic characteristics, prevalence of underlying conditions, hospital admission, ICU admissions, invasive mechanical ventilation usage, readmission, and associated costs for resource utilization. Patient and cost data are presented as average and 95% confidence interval (CI) or frequency distribution and percentages where appropriate. Bootstrapping of cost values was performed using 10,000 samples. The χ^2-test was utilized to compare age, sex, and body mass index (BMI) distribution between the two groups, while for categorical variables, prevalence proportions were calculated and the χ^2-test was employed to detect significant differences. Student's *t*-test was applied to compare the average costs of hospital inpatient stay between SA-SSI cases and controls. Single-factor analysis of variance was applied to test statistical significance of the mean values of cost variables between France, Germany, Spain, and the UK. Additionally, linear regression analysis was performed to evaluate factors associated with increased costs following surgery and the length of inpatient treatment, with both univariable and multivariable analyses utilized to identify significant associations. All statistical analyses, tables, listings, and graphics were conducted using SPSS (IBM Corporation, Chicago, IL, USA).

Results

Patient characteristics

Among the 178,904 patients who underwent surgery in sites in five European countries in 2016, a total of 764 individuals developed SA-SSI. Of these patients, we matched 744 cases to 744 controls, and these matched pairs were included in the subsequent analysis. Due to the absence of health economic data from Italian centres, Italy was not included in the health economic assessment. In terms of demographic characteristics, the age distribution between the cases and controls was found to be similar ($P = 0.704$). The distribution of sex ($P = 0.604$) and body mass index ($P = 0.767$) was also evenly distributed between the two groups. Regarding underlying medical conditions, the most prevalent ones included chronic cardiovascular disease (cases: $N = 172/744$, 23.1%; controls: $N = 163/744$, 21.9%), solid tumour (cases: $N = 166/744$, 22.3%; controls: $N = 116/744$, 15.6%), and diabetes mellitus (cases: $N = 156/744$, 21.0%; controls: $N = 131/744$, 17.6%). Significant statistical differences were observed in peripheral venous disease ($P = 0.012$) and solid tumour prevalence ($P = 0.001$), both of which were more common in the SA-SSI cases. Conversely, hemiplegia was found to be more common in the control group ($P = 0.033$) (Table I) [12].

Table I
Demographics of cases and controls[a]

Variable	Cohort	SA-SSI cases	Controls	P-value (SA-SSI cases vs controls)
Age (% (N)) (years)	56.7	58.1 (range: 18–95)	57.7 (range: 18–97)	NS
18–29	9.5 (17,056/178,902)	9.5 (71/744)	11.4 (85/744)	
30–44	19.0 (33,967/178,902)	16.7 (124/744)	17.1 (127/744)	
45–59	23.3 (41,728/178,902)	20.4 (152/744)	19.6 (146/744)	
60–75	30.2 (53,981/178,902)	34.3 (255/744)	30.9 (230/744)	
>75	17.98 (32,170/178,902)	19.1 (142/744)	21.0 (156/744)	
Sex (% (N))				NS
Female	51.7 (92,468/178,902)	48.1 (358/744)	46.6 (347/744)	
Male	48.3 (86,434/178,902)	51.9 (386/744)	53.4 (397/744)	
BMI (% (N))	n/a			NS
<18.5		1.9 (12/625)	2.2 (13/593)	
18.5–24.9		32.3 (204/625)	44.4 (263/593)	
25.0–29.9		34.4 (215/625)	32.5 (193/593)	
30.0–34.9		20.8 (130/625)	15.3 (91/593)	
35.0–39.9		6.9 (43/625)	4.0 (24/593)	
>40		3.4 (21/625)	1.5 (9/593)	
Comorbidities (% (N))				
Cardiovascular				
Chronic CVD	4.39 (4,454/101,410)	23.1 (172/744)	21.9 (163/744)	NS
Congestive HF	1.07 (1,082/101,410)	7.7 (57/744)	5.5 (41/744)	NS
Peripheral VD	3.43 (3,482/101,410)	12.1 (90/744)	8.1 (60/744)	0.012
Pulmonary				
COPD	1.45 (1,475/101,410)	6.2 (46/744)	4.4 (33/744)	NS
Cancer				
Leukaemia	0.15 (154/101,410)	0.4 (3/744)	0.3 (2/744)	NS
Lymphoma	0.28 (285/101,410)	2.2 (16/744)	0.9 (7/744)	NS
Solid tumour	7.29 (7,396/101,410)	22.3 (166/744)	15.6 (116/744)	0.001
Neurological				
Dementia	0.32 (321/101,410)	2.3 (17/744)	2.4 (18/744)	NS
TIA or CVA	0.13 (132/101,410)	5.8 (43/744)	5.8 (43/744)	NS
Hemiplegia	0.89 (904/101,410)	1.3 (10/744)	3.1 (23/744)	0.033
Other comorbidities				
Diabetes	11.43 (11,591/101,410)	21.0 (156/744)	17.6 (131/744)	NS
Liver disease	1.12 (1,138/101,410)	4.4 (33/744)	5.0 (37/744)	NS
CKD	3.22 (3,271/101,410)	7.8 (58/744)	7.0 (52/744)	NS
Other				
HIV/AIDS	0.09 (96/101,410)	1.2 (9/744)	0.8 (6/744)	NS

SA, *Staphylococcus aureus*; SSI, surgical site infection; NS, non-significant; BMI, body mass index; CVD, cardiovascular disease; HF, heart failure; VD, vascular disease; COPD, chronic obstructive pulmonary disease; TIA, transient ischaemic attack; CVA, cerebrovascular accident; CKD, chronic kidney disease; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome.
[a] Source: Table I from Mellingford *et al*. [12].

Among the 744 observed cases of SA-SSI, a substantial majority of 727/744 (97.7%) required immediate hospital admission following surgery, incurring an average cost of €8,810 (95% CI: 7,947–9,673). By contrast, controls without infections showed a lower admission rate, with 704 out of 744 cases (94.6%) requiring hospitalization, and associated average costs of €6,032 (5,394–6,671). The disparity in both admission rates ($P = 0.030$) and related costs ($P < 0.001$) between the cases and controls was statistically significant. Subsequent to the initial hospital admission, 147 out of 724 SA-SSI cases (20.3%) necessitated admission to an ICU, compared to 128 out of 704 controls (18.2%), with no statistically significant difference observed between the two groups. However, SA-SSI cases exhibited a higher rate of invasive mechanical ventilation after ICU admission (*N* cases = 67/147, 45.6%; *N* controls = 37/128, 28.9%), with this difference being statistically significant in terms of proportions ($P = 0.003$), though not in terms of costs. Regarding readmission proportion within the 12 months following surgery, this was reported in 374/744 SA-SSI cases (50.3%) compared to 185/744 controls (24.9%), with a statistically significant difference ($P < 0.001$). Moreover, the costs associated with these readmissions were higher in SA-SSI cases, with an average cost of €7,962 (6,672–9,251), as compared to controls with an average cost of €5,299 (4,077–6,520), which was statistically significant ($P = 0.005$) (Table II).

Data on surgery-related costs and the length of specialized healthcare in the hospital are shown in Table III. In the univariable analysis, there were significant associations between

Table II
Overall costs of treatment of SA-SSI cases/controls and components of cost

Variable	Overall		SA-SSI cases		Controls		*P*-value (SA-SSI cases vs controls)	
	N	Costs (€) average (95% CI)	*N*	Costs (€) average (95% CI)	*N*	Costs (€) average (95% CI)	*P* (*N* values)	*P* (costs)
Postoperative hospitalization	1438	7,440.6 (6,897.6–7,983.6)	727	8,809.9 (7,947.1–9,672.7)	711	6,032.4 (5,394.2–6,670.5)	0.030	<0.001
1st ICU admission <1 year post surgery	275	14,279.6 (11,960.1–16,599.1)	147	14,330.2 (11,063.5–17,597.0)	128	14,221.4 (10,894.0–17,548.7)	NS	NS
1st ICU admission <1 year post surgery, with MV	104	1,911.8 (1,138.7–2,684.8)	67	2,123.9 (1,042.5–3,205.3)	37	1,506.2 (555.8–2,456.6)	0.003	NS
2nd ICU admission <1 year post surgery	23	14,078.5 (7,762.5–20,394.6)	16	12,116.4 (5,078.8–19,154.0)	7	18,563.5 (2,216.4–34,910.5)	NS	NS
2nd ICU admission <1 year post surgery, with MV	6	1,915.8 (−844.1–4,675.6)	3	1,944.3 (−5,999.6–9,888.1)	3	1,887.3 (−4,713.9–8,488.4)	NS	NS
Hospital readmission <1 year post surgery	559	7,080.3 (6,124.0–8,036.6)	374	7,961.6 (6,671.9–9,251.3)	185	5,298.6 (4,077.3–6,519.9)	<0.001	0.005
Hospital readmission <1 year post surgery with ICU	46	11,959.1 (7,673.5–16,244.8)	34	12,356.5 (7,222.7–17,490.3)	12	10,833.2 (1,832.6–19,833.7)	0.001	NS
Hospital readmission <1 year post surgery with ICU and MV	16	807.2 (371.9–1,242.5)	12	881.7 (291.3–1,472.0)	4	602.5 (−166.1 to 1,371.1)	NS	NS
Overall	1488	12,657.1 (11,643.4–13,670.8)	744	15,667.2 (14,106.6–17,227.8)	744	9,646.9 (8,385.8–10,908.0)	–	<0.001

SA, *Staphylococcus aureus*; SSI, surgical site infection; ICU, intensive care unit; NS, non-significant; MV, invasive mechanical ventilation.

Table III
Regression analysis of what the cost drivers were in the total cohort

Overall costs/days	Univariable				Multivariable			
	β regression coefficient	R^2	*P*-value	95% CI	β regression coefficient	R^2	*P*-value	95% CI
Overall costs								
Postoperative hospitalization	1.476	0.586	<0.001	(1.412–1.541)	1.062	0.642	<0.001	(1.034–1.090)
1st ICU admission <1-year post-surgery	1.317	0.663	<0.001	(1.205–1.429)	0.940	0.352	<0.001	(0.895–0.985)
1st ICU admission <1-year post-surgery, with MV	5.194	0.285	<0.001	(3.534–6.853)				
2nd ICU admission <1-year post-surgery	2.101	0.438	0.001	(1.021–3.181)				
2nd ICU admission <1-year post-surgery, with MV	2.629	0.014	NS	(−28.154 to 33.412)				
Hospital readmission <1-year post-surgery	1.284	0.436	<0.001	(1.163–1.406)	0.989	0.425	<0.001	(0.956–1.021)
Hospital readmission <1-year post-surgery with ICU	1.524	0.391	<0.001	(0.947–2.102)				
Hospital readmission <1-year post-surgery with ICU and MV	6.140	0.017	0.643	(−21.809 to 34.089)				
Overall days								
Postoperative hospitalization	1.213	0.862	<0.001	(1.175–1.250)	1.167	0.454	<0.001	(1.086–1.248)
1st ICU admission <1-year post-surgery	1.837	0.704	<0.001	(1.616–2.057)	0.961	0.556	<0.001	(0.907–1.014)
1st ICU admission <1-year post-surgery, with MV	0.104	0.580	<0.001	(0.075–0.133)				
2nd ICU admission <1-year post-surgery	2.393	0.481	0.020	(0.416–4.369)				
2nd ICU admission <1-year post-surgery, with MV	87.240	0.232	NS	(−419.530 to 594.011)				
Hospital readmission <1-year post-surgery	1.197	0.653	<0.001	(1.081–1.312)	1.005	0.440	<0.001	(0.939–1.071)
Hospital readmission <1-year post-surgery with ICU	1.595	0.342	0.020	(0.264–2.926)				
Hospital readmission <1-year post-surgery with ICU and MV	0.050	0.071	NS	(−0.371 to 0.471)				

R^2, coefficient of determination; CI, confidence interval; ICU, intensive care unit; MV, invasive mechanical ventilation; NS, non-significant.

Table IV
Country comparison: surgical site infection cases

Variable	France		Germany		Spain		UK		*P*-value (*N* values)	*P*-value (costs)
	N	Costs (€) average (95% CI)	*N*	Costs (€) average (95% CI)	*N*	Costs (€) average (95% CI)	*N*	Costs (€) average (95% CI)		
Postoperative hospitalization	209	8,647.2 (7,222.6–10,071.8)	172	7,173.0 (6,146.2–8,199.8)	179	15,415.7 (12,842.0–17,989.3)	167	3,626.5 (2,836.2–4,416.8)	0.001	<0.001
1st ICU admission <1 year post surgery	40	19,727.6 (13,450.5–26,004.7)	69	12,489.8 (7,322.9–17,656.7)	33	11,206.7 (5,297.5–17,115.9)	5	17,164.3 (−6,939.8–41,268.5)	<0.001	NS
1st ICU admission <1 year post surgery, with MV	21	1,106.6 (348.6–1,864.7)	32	2,030.7 (639.2–3,422.2)	13	2,954.9 (−1,141.1–7,050.9)	1	–	<0.001	0.033
2nd ICU admission <1 year post surgery	6	20,084.0 (1,764.5–38,403.4)	6	5,475.7 (1,395.6–9,555.9)	4	10,126.0 (−7,204.8–27,456.8)	0	–	NS	NS
2nd ICU admission <1 year post surgery, with MV	2	98.0 (−15.2 to 211.2)	0	–	1	–	0	–	NS	–
Hospital readmission <1 year post surgery	143	11,240.7 (8,356.4–14,125.0)	93	4,726.7 (3,653.2–5,800.3)	91	9,159.4 (7,016.1–11,302.7)	47	2,066.4 (1,124.4–3,008.3)	<0.001	<0.001
Hospital readmission <1 year post surgery with ICU	19	16,571.8 (8,173.4–24,970.3)	11	5,628.9 (1,228.2–10,029.6)	3	12,327.3 (−21,840.1–46,494.8)	1	–	<0.001	NS
Hospital readmission <1 year post surgery with ICU and MV	6	953.3 (31.1–1,875.5)	5	955.4 (−708.9 to 2,619.8)	1	–	0	–	0.025	NS
Overall	420	20,550.7 (16,994.8–24,106.7)	344	14,930.2 (11,966.4–17,894.0)	374	21,325.3 (18,009.3–24,641.2)	1488	4,485.4 (3,414.0–5,556.7)	–	<0.001

CI, confidence interval; ICU, intensive care unit; MV, invasive mechanical ventilation; NS, non-significant.

increased surgery-related costs and cost of hospitalization immediately after surgery (odds ratio (OR): 1.476; 95% CI: 1.412–1.541), first ICU admission within 12 months since surgery overall (1.317; 1.205–1.429), and first ICU admission within 12 months since surgery with invasive mechanical ventilation (5.194; 3.534–6.853), second ICU admission within 12 months since surgery (2.101; 1.021–3.181), hospital readmission within 12 months since surgery overall (1.284; 1.163–1.406), and hospital readmission within 12 months since surgery with ICU (1.524; 0.947–2.102). In the multivariable analysis, cost of hospitalization immediately after surgery (adjusted odds ratio (aOR): 1.062; 1.034–1.090), first ICU admission within 12 months since surgery overall (0.940; 0.895–0.985), and hospital readmission within 12 months since surgery overall (0.989; 0.956–1.021) remained significant.

Regarding the increased length of specialized healthcare in the hospital, the univariable analysis revealed associations with days of hospitalization immediately after surgery (OR: 1.213; 95% CI: 1.175–1.250), days of first ICU admission within 12 months since surgery overall (1.837; 1.616–2.057), hours with invasive mechanical ventilation (0.104; 0.075–0.133), days of second ICU admission within 12 months since surgery (2.393; 0.416–4.369), days of hospital readmission within 12 months since surgery overall (1.197; 1.081–1.312), and days in ICU (1.595; 0.264–2.926). In the multivariable analysis, the length of specialized healthcare was significantly associated with increased number of days of hospitalization immediately after surgery (aOR: 1.167, 95% CI 1.086–1.248), days of first ICU admission within 12 months since surgery overall (0.961; 0.907–1.014), and days of hospital readmission within 12 months since surgery overall (1.005; 0.939–1.071) (Table III).

The comparative cost analysis of postoperative outcomes in four European countries revealed substantial variations. For postoperative hospitalization, Spain exhibited the highest average cost at €15,416 (95% CI: €12,842–17,989), significantly surpassing France (€8,647; 7,223–10,072), Germany (€7,173; 6,146–8,200), and the UK (€3,627; 2,836–4,417) ($P <$ 0.001). Notable differences persisted in first ICU admission within one year post surgery, with significantly higher costs observed in France and the UK ($P = 0.003$). The analysis extends to specific scenarios, such as ICU admission with invasive mechanical ventilation, showcasing diverse cost patterns. Hospital readmission costs within the first year post surgery also exhibited significant disparities ($P < 0.001$) (Table IV).

Discussion

The health economic analyses conducted in our study provide insights into the substantial burden imposed by SA-SSI on healthcare systems. The findings from this large-scale study underscore the urgent need for efficient infection prevention strategies to minimize the impact of SA-SSI on hospital resources and healthcare expenditures.

Most concerningly, we report significantly higher rates of hospitalization immediately after surgery in SA-SSI cases. This is also reflected by higher costs and highlights the critical importance of early detection and timely management of SA-SSI, or in best case prevention. Hereby, prolonged hospital stays and costly interventions may be reduced [24,25]. The possibility of delayed diagnosis leading to more severe infections in SA-SSI cases warrants further investigation. Implementing evidence-based infection control measures for SSI prevention, such as preoperative screening for colonization, promoting aseptic techniques during surgery, and administering appropriate antimicrobial prophylaxis, becomes pivotal in reducing the incidence of SA-SSI and minimizing the subsequent economic burden [26–29]. Our result of mean overall costs of €15,667 (14,107–17,228) per SA-SSI is in line with other health economic evaluations analysing the burden of SA-SSI in Switzerland and the UK [7,9]. Nevertheless, it should be noted that comparability of health economic analyses is sometimes limited due to differences in study designs, e.g. different perspectives used, the consideration of cost factors, different cost values for inpatient care, and different observational periods.

Moreover, the higher proportion of SA-SSI cases requiring ICU admission and invasive mechanical ventilation emphasizes the severity of these infections and their potential to escalate into critical conditions. The need for invasive mechanical ventilation in SA-SSI cases may be indicative of more aggressive disease progression, higher morbidity, or underlying respiratory complications. This finding underscores the significance of vigilant monitoring and prompt management of SA-SSI cases to prevent complications that may necessitate ICU care [27–30]. Early intervention and comprehensive infection control measures in surgical units and ICU can potentially reduce the burden of critical care resources and mitigate the substantial healthcare costs associated with managing severe SA-SSI cases.

Beyond the immediate postoperative impact, our study unveils a concerning trend of higher readmission rates among SA-SSI cases, accompanied by significantly elevated healthcare costs. This indicates the long-term consequences of SA-SSI that extend beyond the initial hospital stay. The reasons for these readmissions warrant thorough investigation. It is plausible that SA-SSI cases may experience more post-discharge complications, recurrences, other wound-related issues, or delayed recovery, necessitating readmissions for further medical attention [31–33]. The significance of post-discharge surveillance, appropriate wound care, and follow-up interventions cannot be overstated. Developing effective strategies for transitional care and enhanced patient education is paramount to reducing readmission rates, improving patient outcomes, and alleviating the health economic burden on healthcare systems.

While our study yields valuable insights, several limitations should be acknowledged. The cross-sectional nature of our study design restricts our ability to establish causal relationships between patient characteristics, SA-SSI, and economic outcomes. Future prospective, longitudinal studies would be valuable in elucidating temporal associations and exploring potential causality. Additionally, the lack of detailed clinical data, such as the severity of SA-SSI cases, microbiological information, or specific patient outcomes hampers a more nuanced analysis of the underlying mechanisms driving the observed associations. Due to the study design, it was not possible to calculate drug administration costs of patients with SA-SSI, which might have led to a conservative underrepresentation of overall costs associated with SA-SSI. It should be noted that this likely results in an underestimation of overall resource utilization and costs. Obtaining comprehensive clinical data, including microbiological profiles and SSI classifications, could enhance our understanding of the pathophysiology of SA-SSI and its economic impact. Finally, a notable limitation is the temporal gap inherent in this study, relying on data from 2016, a period predating the pandemic. The evident evolution in working methodologies, global inflation crisis, clinical pathways, infection prevention and control practices, and advancements in surgical theatre technology since then raises the possibility of a disconnect between the study's findings and the current healthcare landscape. Therefore, acknowledging the dynamic nature of the healthcare environment, a repetition of the analysis in the current post-pandemic situation could provide valuable insights for the scientific community.

In conclusion, our study provides critical insights into the economic consequences of SA-SSI and emphasizes the urgent need for effective infection prevention strategies. The higher rates of hospitalization, ICU admissions, and readmissions among SA-SSI cases underscore the severity of these infections and their impact on healthcare costs. By implementing evidence-based infection control measures, promoting early detection, and improving patient care, healthcare systems can optimize resource utilization, improve patient outcomes, and ultimately reduce the economic burden of SA-SSI. Future research with longitudinal and more comprehensive data can further enhance our understanding and inform targeted interventions to combat SA-SSI and its associated economic implications effectively, contributing to improved patient care and optimized healthcare resource allocation.

Data availability

Data are available upon reasonable request to the corresponding author.

Author contributions

J.S.G., S.C.M., B.L., O.A.C., and S.W.H. designed and conceived the study idea and verified cohort and case–control data. B.L. performed matching of cases and controls. J.S.G. and S.W.H. performed the economic analyses and wrote the first draft of the manuscript. All authors supported the writing of the final version of the manuscript.

Conflict of interest statement

J. Salmanton-García reports speaker honoraria from Gilead and Pfizer, and Advisory Board from Pfizer, outside of the submitted work. C. Bruns reports no conflicts of interest regarding the submitted work; now is an employee for Milteny Biontech. Th. Guimard reports personal fees from Pfizer, Gilead and Viiv healthcare, outside of the submitted work. A. Soriano reports grants from Pfizer, grants from Merck Sharp Dhome, grants from Gilead, personal fees from Menarini, personal fees from Angelini, personal fees from Shionogy, outside the submitted work. M.W. Pletz reports grants for the German Research Foundation, the German Ministry for Education and Research, grants and personal fees from Pfizer, personal fees from MSD, personal fees from Infectopharm, personal fees from Thermofisher, personal fees from Shionogi, personal fees from Angelini, personal fees from Chiemsi, personal fees from Novartis, outside the submitted work. H. Seifert reports grants from German Centre for Infection Research (DZIF), personal fees from Basilea Pharmaceuticals, personal fees from Gilead, personal fees from MSD, personal fees from Entasis, grants from Accelerate, personal fees from Shionogi, personal fees from ThermoFisher, personal fees from bioMérieux, personal fees from Becton Dickinson, personal fees from Shionogi, personal fees from Eumedica, outside the submitted work. O.A. Cornely reports grants or contracts from Amplyx, Basilea, BMBF, Cidara, DZIF, EU-DG RTD (101037867), F2G, Gilead, Matinas, MedPace, MSD, Mundipharma, Octapharma, Pfizer, Scynexis; consulting fees from Abbvie, Amplyx, Biocon, Biosys, Cidara, Da Volterra, Gilead, IQVIA, Janssen, Matinas, MedPace, Menarini, Molecular Partners, MSG-ERC, Noxxon, Octapharma, Pfizer, PSI, Scynexis, Seres; honoraria for lectures from Abbott, Abbvie, Al-Jazeera Pharmaceuticals, Astellas, Gilead, Grupo Biotoscana/United Medical/Knight, Hikma, MedScape, MedUpdate, Merck/MSD, Mylan, Noscendo, Pfizer, Shionogi; payment for expert testimony from Cidara; participation on a Data Safety Monitoring Board or Advisory Board from Actelion, Allecra, Cidara, Entasis, IQVIA, Janssen, MedPace, Paratek, PSI, Pulmocide, Shionogi, The Prime Meridian Group, outside of the submitted work. S.C. Mellinghoff reports grants from University of Cologne (KoelnFortune), grants from Dr Manfred Plempel Stipend, grants from DZIF Clinical Leave, personal fees from Octapharma, outside the submitted work. M.W. Pletz reports grants for the German Research Foundation, the German Ministry for Education and Research, grants and personal fees from Pfizer, personal fees from MSD, personal fees from Infectopharm, personal fees from Thermofisher, personal fees from Shionogi, personal fees from Angelini, personal fees from Chiemsi, personal fees from Novartis, outside the submitted work. B.J. Liss reports grants from Pfizer, during the conduct of the study. S.M. Wingen-Heimann received research and travel grants from Astellas and Merck; research grants from Basilea, Gilead, and 3M; travel grants from Pfizer and Tillotts; lecture honoraria from Astellas and Merck; and is a consultant to Basilea, Gilead, Merck, and Tillotts, outside of the submitted work. Other authors declare no conflicts of interest.

Funding sources

This project was funded by Pfizer (WI212601). As an investigator-initiated trial, the sponsor therefore was the University of Cologne, which had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

References

[1] European Centre for Disease Prevention and Control. Surveillance of surgical site infections and prevention indicators in European hospitals – HAI-Net SSI protocol, version 2.2. Stockholm: ECDC; 2017.

[2] Zarb P, Coignard B, Griskeviciene J, Muller A, Vankerckhoven V, Weist K, et al. The European Centre for Disease Prevention and Control (ECDC) pilot point prevalence survey of healthcare-associated infections and antimicrobial use. Euro Surveill 2012;17(46):20316.

[3] Anon. New MRSA guidelines highlight a dearth of evidence. Lancet Infect Dis 2011;11:153.

[4] de Lissovoy G, Fraeman K, Hutchins V, Murphy D, Song D, Vaughn BB. Surgical site infection: incidence and impact on hospital utilization and treatment costs. Am J Infect Control 2009;37:387–97.

[5] Boltz MM, Hollenbeak CS, Julian KG, Ortenzi G, Dillon PW. Hospital costs associated with surgical site infections in general and vascular surgery patients. Surgery 2011;150:934–42.

[6] Schweizer ML, Cullen JJ, Perencevich EN, Vaughan Sarrazin MS. Costs associated with surgical site infections in Veterans Affairs hospitals. JAMA Surg 2014;149:575–81.
[7] Coello R, Charlett A, Wilson J, Ward V, Pearson A, Borriello P. Adverse impact of surgical site infections in English hospitals. J Hosp Infect 2005;60:93–103.
[8] Leaper DJ, van Goor H, Reilly J, Petrosillo N, Geiss HK, Torres AJ, et al. Surgical site infection – a European perspective of incidence and economic burden. Int Wound J 2004;1:247–73.
[9] Weber WP, Zwahlen M, Reck S, Feder-Mengus C, Misteli H, Rosenthal R, et al. Economic burden of surgical site infections at a European university hospital. Infect Control Hosp Epidemiol 2008;29:623–9.
[10] Urban JA. Cost analysis of surgical site infections. Surg Infect (Larchmt) 2006;7(Suppl 1):S19–22.
[11] Mellinghoff SC, Bruns C, Al-Monajjed R, Cornely FB, Grosheva M, Hampl JA, et al. Harmonized procedure coding system for surgical procedures and analysis of surgical site infections (SSI) of five European countries. BMC Med Res Methodol 2022;22:225.
[12] Mellinghoff SC, Bruns C, Albertsmeier M, Ankert J, Bernard L, Budin S, et al. *Staphylococcus aureus* surgical site infection rates in 5 European countries. Antimicrob Resist Infect Control 2023;12:104.
[13] Heimann SM, Biehl LM, Vehreschild JJ, Franke B, Cornely OA, Vehreschild M. Chlorhexidine-containing dressings in the prevention of central venous catheter-related bloodstream infections: a cost and resource utilization analysis. Am J Infect Control 2018;46:992–7.
[14] Heimann SM, Penack O, Heinz WJ, Rachow T, Egerer G, Kessel J, et al. Intravenous and tablet formulation of posaconazole in antifungal therapy and prophylaxis: a retrospective, non-interventional, multicenter analysis of hematological patients treated in tertiary-care hospitals. Int J Infect Dis 2019;83:130–8.
[15] Heimann SM, Vehreschild M, Cornely OA, Heinz WJ, Grüner B, Silling G, et al. Healthcare burden of probable and proven invasive mucormycosis: a multi-centre cost-of-illness analysis of patients treated in tertiary care hospitals between 2003 and 2016. J Hosp Infect 2019;101:339–46.
[16] Salmanton-García J, Busca A, Cornely OA, Corradini P, Hoenigl M, Klimko N, et al. EPICOVIDEHA: a ready to use platform for epidemiological studies in hematological patients with COVID-19. Hemasphere 2021;5:e612.
[17] Salmanton-García J, Marchesi F, Itri F, Farina F, Hoenigl M, Córdoba R, et al. Unveiling the hidden burden: from EPICOVIDEHA to EPIFLUEHA, exploring the epidemiology of respiratory viral infections in hematological patients. Hemasphere 2023;7:e970.
[18] Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. Value Health 2022;25:3–9.
[19] Graf von der Schulenburg JM, Greiner W, Jost F, Klusen N, Kubin M, Leidl R, et al. German recommendations on health economic evaluation: third and updated version of the Hanover Consensus. Value Health 2008;11:539–44.
[20] Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 4th ed. Oxford: Oxford University Press; 2015.
[21] Koechlin F, Konijn P, Lorenzoni L, Schreyer P. Comparing hospitals and health prices and volumes across countries: a new approach. Soc Indic Res 2017;131:43–64.
[22] Lorenzoni L, Dougherty S. Understanding differences in health care spending: a comparative study of prices and volumes across OECD countries. Health Serv Insights 2022;15: 11786329221109755.
[23] Wingen-Heimann SM, Davies K, Viprey VF, Davis G, Wilcox MH, Vehreschild MJGT, et al. *Clostridioides difficile* infection (CDI): a pan-European multi-center cost and resource utilization study, results from the Combatting Bacterial Resistance in Europe CDI (COMBACTE-CDI). Clin Microbiol Infect 2023;29:651 e1–e8.
[24] Fenny AP, Asante FA, Otieku E, Bediako-Bowan A, Enemark U. Attributable cost and extra length of stay of surgical site infection at a Ghanaian teaching hospital. Infect Prev Pract 2020;2:100045.
[25] Badia JM, Casey AL, Petrosillo N, Hudson PM, Mitchell SA, Crosby C. Impact of surgical site infection on healthcare costs and patient outcomes: a systematic review in six European countries. J Hosp Infect 2017;96:1–15.
[26] Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation 2007;115:1285–95.
[27] Miles F, Voss L, Segedin E, Anderson BJ. Review of *Staphylococcus aureus* infections requiring admission to a paediatric intensive care unit. Arch Dis Childh 2005;90:1274–8.
[28] Spagnolo AM, Ottria G, Amicizia D, Perdelli F, Cristina ML. Operating theatre quality and prevention of surgical site infections. J Prev Med Hyg 2013;54:131–7.
[29] Calderwood MS, Anderson DJ, Bratzler DW, Dellinger EP, Garcia-Houchins S, Maragakis LL, et al. Strategies to prevent surgical site infections in acute-care hospitals: 2022 update. Infect Control Hosp Epidemiol 2023;44:695–720.
[30] Sampedro GR, Bubeck Wardenburg J. *Staphylococcus aureus* in the intensive care unit: are these golden grapes ripe for a new approach? J Infect Dis 2017;215(Suppl 1):S64–70.
[31] McGarry SA, Engemann JJ, Schmader K, Sexton DJ, Kaye KS. Surgical-site infection due to *Staphylococcus aureus* among elderly patients: mortality, duration of hospitalization, and cost. Infect Control Hosp Epidemiol 2004;25:461–7.
[32] Hardtstock F, Heinrich K, Wilke T, Mueller S, Yu H. Burden of *Staphylococcus aureus* infections after orthopedic surgery in Germany. BMC Infect Dis 2020;20:233.
[33] Primo MG, Guilarde AO, Martelli CM, Batista LJ, Turchi MD. Healthcare-associated *Staphylococcus aureus* bloodstream infection: length of stay, attributable mortality, and additional direct costs. Braz J Infect Dis 2012;16:503–9.