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Original Article

Surgical site infection in hepatobiliary surgery patients and its relationship with serum vitamin D concentration[☆]



Estefania Laviano,^{a,*} María Sanchez,^a María Teresa González-Nicolás,^a María Pilar Palacian,^b Javier López,^c Yolanda Gilaberte,^d Pilar Calmarza,^e Antonio Rezusta,^b Alejandro Serrablo^a

^a Servicio de Cirugía General y Digestiva, Hospital Miguel Servet, Zaragoza, Spain

^b Servicio de Microbiología, Hospital Miguel Servet, Zaragoza, Spain

^c Medicina Familiar y Comunitaria, Sector II, Zaragoza, Spain

^d Servicio de Dermatología, Hospital Miguel Servet, Zaragoza, Spain

^e Servicio de Bioquímica, Hospital Miguel Servet, Zaragoza, Spain

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A B S T R A C T

Introduction: While several studies have examined the correlation between vitamin D concentrations and post-surgical nosocomial infections, this relationship has yet to be characterized in hepatobiliary surgery patients. We investigated the relationship between serum vitamin D concentration and the incidence of surgical site infection (SSI) in patients in our hepatobiliary surgery unit.

Methods: Participants in this observational study were 321 successive patients who underwent the following types of interventions in the hepatobiliary surgery unit of our center over a 1-year period: cholecystectomy, pancreaticoduodenectomy, total pancreatectomy, segmentectomy, hepatectomy, hepaticojejunostomy and exploratory laparotomy. Serum vitamin D levels were measured upon admission and patients were followed up for 1 month. Mean group values were compared using a Student's T-test or Chi-squared test. Statistical analyses were performed using the Student's T-test, the Chi-squared test, or logistic regression models.

Results: Serum concentrations >33.5 nmol/l reduced the risk of SSI by 50%. Out of the 321 patients analyzed, 25.8% developed SSI, mainly due to organ-cavity infections (incidence, 24.3%). Serum concentrations of over 33.5 nmol/l reduced the risk of SSI by 50%.

Conclusions: High serum levels of vitamin D are a protective factor against SSI (OR, 0.99). Our results suggest a direct relationship between serum vitamin D concentrations and SSI, underscoring the need for prospective studies to assess the potential benefits of vitamin D in SSI prevention.

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* Corresponding author.

E-mail address: estefania.laviano@gmail.com (E. Laviano).

Infección del sitio quirúrgico en cirugía hepatobiliopancreática y su relación con la concentración sérica de vitamina D

R E S U M E N

Palabras clave:

Cirugía hepatobiliopancreática
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Introducción: La relación entre las infecciones nosocomiales en pacientes quirúrgicos y la vitamina D ha sido estudiada por algunos autores. Sin embargo, hasta la fecha no existe ningún estudio realizado sobre pacientes de cirugía hepatobiliar. El objetivo de nuestro trabajo es estudiar la infección del sitio quirúrgico (ISQ) en la unidad de cirugía hepatobiliar, y valorar su relación con la concentración sérica de vitamina D.

Métodos: Se llevó a cabo un estudio analítico observacional de pacientes sucesivos intervenidos en la unidad de cirugía hepatobiliar de nuestro centro durante un año. Se incluyeron las intervenciones relativas a enfermedad biliar, pancreática y hepática. Se determinaron los niveles de vitamina D al ingreso, así como las ISQ de tipo superficial, profunda y Organ/space diagnosticadas durante el estudio. El seguimiento del paciente se realizó durante al menos un mes tras la cirugía, dependiendo de la enfermedad. La estadística se realizó mediante el programa estadístico R v.3.1.3.

Resultados: La muestra quedó constituida por 321 pacientes, de los cuales el 25,8% presentó ISQ a expensas fundamentalmente de las infecciones Organ/spaces que presentaron una incidencia del 24,3%. Concentraciones séricas superiores a 33,5 nmol/l demostraron reducir en un 50% el riesgo de ISQ.

Conclusiones: Las concentraciones elevadas de vitamina D en sangre demostraron ser un factor protector frente a las ISQ (OR: 0,99). Nuestros resultados sugieren una relación directa entre la concentración sérica de vitamina D y la ISQ, justificando la realización de nuevos estudios prospectivos.

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Introduction

Hepatobiliary surgery is a highly complex type of surgery from both a technical and anesthetic standpoint. Morbidity rates after liver surgery range from 17% in benign disease to 27% in malignant disease, with mortality rates close to 5%.¹

As for pancreatic resections, overall morbidity rates range between 50% and 60% (59% for pancreatic head resection, 35% for distal resection and 46.7% for total pancreatectomy), depending on the series. The most frequent complications are collections (15.4%) and intra-abdominal abscesses (13.7%). In these procedures, overall mortality is around 3%.^{2,3}

In 2018, Takahashi et al. published a study analyzing the risk factors for surgical site infection (SSI)⁴ after liver and pancreatic surgery in 735 patients, obtaining a total SSI rate of 17.8%. The interventions with the highest incidence of SSI were hepatectomies with bile duct resection (39.1%), pancreaticoduodenectomies (28.8%) and distal pancreatectomies (29.8%).⁵ A higher prevalence of the organ/space type was registered, with rates ranging from 25.1% in major hepatectomies to 39.1% in the case of pancreaticoduodenectomies.⁶

As for cholecystectomy, SSI rates are around 7% in open surgery and barely 1% in elective laparoscopic surgery.^{5,7}

Currently, initiatives like Enhanced Recovery After Surgery (ERAS) seek to improve patients' preoperative conditions and to improve recovery with the multidisciplinary application of a series of surgical and anesthetic measures.¹

Vitamin D has been studied by certain authors for the prevention of nosocomial infections due to its influence on

immune system function, since its receptors are expressed by macrophages, B and T lymphocytes, and neutrophils. It is also involved in the synthesis of antimicrobial peptides responsible for innate immunity.⁸⁻¹²

In the case of SSI in particular, publications like the Abdehghah AG et al. study have documented that preoperative vitamin D levels have a significant influence on SSI rates and are considered a protective factor.¹²

However, no study has addressed its influence on SSI in hepatobiliary surgery in particular. Therefore, the objective of our study is to study SSI in the hepatobiliary surgery unit of our hospital and assess its relationship with preoperative serum vitamin D concentrations.

Methods

A prospective, analytical, observational study was carried out with consecutive patients treated by the hepatobiliary surgery unit of a tertiary hospital during the period of one year. Approval was obtained for the study from the Aragón Clinical Research Ethics Committee (CEICA), and patients gave their informed consent.

Patients who were admitted to the unit for either urgent or scheduled procedures, with hospital stays longer than 48 h, were included in the study. The surgeries analyzed included: cholecystectomy, segmentectomy, minor hepatectomy (<3 segments), major hepatectomy (> 3 segments), distal pancreatectomy, pancreaticoduodenectomy, total pancreatectomy, exploratory laparotomy, and hepaticojejunostomy.

Serum concentrations of vitamin D were determined in all patients both upon admission and afterwards. Superficial, deep and organ/space SSI diagnosed during the study were monitored, both during hospitalization and at the postoperative follow-up office visits one month after surgery and in some cases until June 2019 if the patients had more than one follow-up appointment.

The following data were collected for all patients included in the study: comorbidities, ASA¹³ and Charlson¹⁴ indices, diagnostic data, treatment, NNIS index,^{4,6} procedural data, results (Clavien-Dindo scale),¹⁵ readmissions, reoperations, ICU admission and stay, total hospital stay, mortality, infection and serum concentrations of vitamin D. The diagnosis of infection was made using CDC criteria.¹⁶

Vitamin D determinations were performed in the clinical biochemistry laboratory at our hospital with an automated immunoassay using Alinity i 25-OH-vitamin D (Abbot, USA).^{17,18}

Following the guidelines of the Spanish Society for Bone Research and Mineral Metabolism (SEIOMM), vitamin D deficiency was defined as a serum concentration between 20–30 ng/ml (50–75 nmol/L), and deficiency was a level less than 20 ng/ml (< 50 nmol/L). Therefore, serum concentrations between 30 and 75 nmol/L were considered normal.^{19–21}

Statistical analysis

With the data obtained, a database was prepared that was subsequently analyzed using R statistical software, version 3.1.3.

After verifying that they followed a normal distribution with the Shapiro-Wilk test, the quantitative variables were expressed with means and standard deviation. The qualitative variables were expressed through the distribution of frequencies in their categories.

Comparisons between means were made using Student's t test (continuous variables) or the chi-square test with a correction for continuity (categorical variables). Odds ratios (OR) were calculated from logistic regression models, with the dependent variable (y) being the occurrence/absence of nosocomial infection, and the independent variable(s) were those that were considered of interest. The Wald test was used to calculate the significance of each coefficient of the model. P values less than .05 were considered statistically significant.

When the group variable had 3 categories, comparisons between means were made by analysis of variance (ANOVA) for continuous variables. The bivariate comparisons (post-hoc) were carried out with the Tukey method for parametric variables or the Benjamini-Hochberg method if the explanatory variable did not have a normal distribution.

For the multivariate analysis of the sample, we decided to divide it into tertiles in order to obtain more balanced groups since its size did not allow for conclusions to be drawn with the divisions of the SEIOMM.

ROC curves were used to determine the sensitivity and specificity of plasma vitamin D concentrations as a predictor of SSI. We chose the cut-off point for vitamin D concentration that maximized specificity and sensitivity.

Results

The sample consisted of 321 patients who fulfilled the inclusion criteria of the study, from whom 301 vitamin D samples were obtained that were suitable for analysis. Twenty samples did not meet the conditions required by the analyzer (4 patients from the liver group, 15 from the gallbladder group and 1 from the pancreas group; none of them infected).

Out of the 321 patients, 178 (55.5%) were men and 143 (44.5%) were women, with a mean age of 65 ± 13 years. Their comorbidities, ASA and Charlson scores are shown in Table 1.

The mean serum concentration of vitamin D, assessed from the 301 viable samples, was 38.3 ± 24.6 nmol/L. More than 76.6% of patients presented <50 nmol/L of vitamin D, which were levels compatible with vitamin D deficiency, and 33.9% were within the lowest tertile (Table 1).

The overall SSI rate was 25.8%, and the interventions with the highest number of registered infections were pancreaticoduodenectomy and total pancreatectomy (29%), cholecystectomy (22%), segmentectomy and minor hepatectomy (<3 segments) (18 %).

SSI were shown to be significantly more prevalent in males ($P = .007$), patients with protein malnutrition ($P < .001$), neoplasms ($P = .011$) and hospitalization in the previous 18 months ($P = .003$). They also proved to be more frequent in patients with ASA III-IV, who constituted 51.8% of the infected group ($P = .001$) and with Charlson scores greater than 4 points (80.7%), although this latter case was not significant ($P = .064$) (Table 1).

The patients with SSI also presented lower concentrations of vitamin D ($P = .012$), with a mean of 33.2 ± 19 nmol/L. This significance was lost when the sample was divided into tertiles; however, the first tertile was constituted by 42.2% of the patients with SSI (Table 1).

When we analyzed the hospital results, patients with SSI had longer stays in the ICU (4.5 ± 7.7 days vs 1.2 ± 3.8 days) and higher rates of readmission, reoperation and mortality ($P < .001$) (Table 1).

Regarding the type of SSI by diagnostic group, organ/space infection was the most frequent in all categories. The most frequently detected microorganisms were *Escherichia coli* and the 'other gram-negative' and 'other gram-positive' agents (Table 2).

With regards to comorbidities in the univariate analysis, protein malnutrition ($P < .001$), neoplasms ($P = .007$) and hospitalization in the last 18 months ($P = .002$) were associated with an increased risk of up to 3 times higher (Table 3). In addition, patients who presented ASA III-IV experienced an SSI risk with nearly a four-fold increase ($P = .002$), as well as patients with high scores on the Charlson index ($P < .001$) and those that required transfusions and vasopressors with almost 5 times the risk.

Scheduled surgery and the laparoscopic approach showed a significant decrease in the risk of SSI ($P = .003$ and $P < .001$). Pancreaticoduodenectomies were the procedure type with the highest increased risk for SSI ($P < .001$).

High concentrations of vitamin D in the blood constituted a protective factor against SSI, presenting on the other hand a low level of significance (OR: 0.99; [0.97–0.99]).

Table 1 – Patient characteristics grouped by the presence of surgical site infection. The percentages that are shown in each category have been calculated in relation to infection.

Variables	Cases, N%			
	Surgical site infection			
	TOTAL N = 321	Negative N = 238	Positive N = 83	P
Demographics				
Sex:				
Men	178 (55.5%)	121 (50.8%)	57 (69%)	0.007
Women	143 (44.5%)	117 (49.2%)	26 (31%)	
Age (yrs) Me ± SD	65 ± 13.1	64 ± 14	67.6 ± 9.60	0.011
Comorbidities				
Diabetes	63 (20%)	49 (21%)	14 (17%)	0.566
COPD	27 (8%)	12 (5.04%)	15 (18%)	0.001
Cardiopathy	55 (17%)	35 (15%)	20 (24%)	0.074
Obesity	85 (27%)	63 (27%)	22 (27%)	1.000
Protein malnutrition	117 (37%)	70 (30%)	47 (57%)	<0.001
Cancer	180 (56%)	123 (52%)	57 (69%)	0.011
Hospitalization last 18 months	224 (69.8%)	155 (65.1%)	69 (83%)	0.003
ASA category:				0.001
1	48 (15%)	41 (17%)	7 (8%)	0.064
2	161 (50.2%)	128 (53.8%)	33 (40%)	
3–4	112 (34.9%)	69 (29%)	43 (52%)	
Charlson Index:				
0	23 (7%)	20 (8%)	3 (4%)	
1	22 (7%)	19 (8%)	3 (4%)	
2	16 (5%)	15 (6%)	1 (1%)	
3	37 (12%)	28 (12%)	9 (11%)	
+4	222 (69.4%)	155 (65.4%)	67 (81%)	
Vitamin D				
Serum concentrations of 25OHD Me ± SD	38.3 ± 24.6	40.2 ± 26.2	33.2 ± 19.0	0.012
Vitamin D categories:				0.471
<50 nmol/L	229 (76.1%)	162 (74.3%)	67 (81%)	0.074
50–75 nmol/L	51 (17%)	39 (18%)	12 (15%)	
>75 nmol/L	21 (7%)	17 (8%)	4 (5%)	
Vitamin D tertiles				
[8.8,25.5]	102 (33.9%)	67 (31%)	35 (42%)	0.074
(25.5,43.3]	99 (33%)	71 (33%)	28 (34%)	
(43.3,233]	100 (33.2%)	80 (37%)	20 (24%)	
Diagnosis				
Diagnosis:				<0.001
Liver metastasis	81 (25%)	67 (28%)	14 (17%)	<0.001
Hepatic cysts	21 (7%)	13 (5%)	8 (10%)	
Liver carcinoma	16 (5%)	15 (6%)	1 (1%)	
Cholangiocarcinoma	18 (6%)	8 (3%)	10 (12%)	
Cholecystitis	28 (9%)	15 (6.%)	13 (16%)	
Cancer, head of pancreas	45 (14%)	19 (8%)	26 (31%)	
Cancer, body-tail of pancreas	13 (4%)	8 (3%)	5 (6%)	
Cholelithiasis	99 (31%)	93 (39%)	6 (7%)	
Treatment				
Type of procedure:				<0.001
Segmentectomy and minor hepatectomy	77 (24%)	62 (26%)	15 (18%)	<0.001
Major hepatectomy	41 (13%)	28 (12%)	13 (16%)	
Pancreaticoduodenectomy	36 (11%)	12 (5%)	24 (29%)	
Total pancreatectomy				
Distal pancreatectomy	11 (3%)	7 (3%)	4 (5%)	
Cholecystectomy	122 (38.0%)	104 (43.7%)	18 (22%)	
Exploratory laparotomy	28 (9%)	22 (9%)	6 (7%)	
Hepaticojejunostomy	6 (2%)	3 (1%)	3 (4%)	
Procedure				
Type:				0.003
Urgent	22 (7%)	10 (4%)	12 (15%)	0.003
Scheduled	299 (93%)	228 (96%)	71 (86%)	

Table 1 (Continued)

Variables	Cases, N%			
	Surgical site infection			P
	TOTAL N = 321	Negative N = 238	Positive N = 83	
Approach:				<0.001
Open	208 (65%)	137 (58%)	71 (86%)	
Laparoscopy	113 (35%)	101 (42%)	12 (15%)	
Duration (minutes) Me $\pm$ SD	199 $\pm$ 94.3	175 $\pm$ 77.4	265 $\pm$ 106	<0.001
NNIS index:				<0.001
0	50 (16%)	48 (20%)	2 (2%)	
1	98 (31%)	86 (36%)	12 (15%)	
2	119 (37.1%)	81 (34%)	38 (46%)	
3	54 (17%)	23 (10%)	31 (37%)	
Transfusions	53 (17%)	24 (10%)	29 (35%)	<0.001
Vasopressors	38 (12%)	16 (7%)	22 (27%)	<0.001
Drainage	204 (65.2%)	126 (55%)	78 (94%)	<0.001
Preoperative biliary prosthesis	31 (10%)	9 (4%)	22 (27%)	<0.001
Hospitalization and results				
ICU stay	129 (40%)	71 (30%)	58 (70%)	<0.001
Days of ICU stay	2.09 $\pm$ 5.30	1.23 $\pm$ 3.86	4.56 $\pm$ 7.67	<0.001
Readmission	32 (10.0%)	10 (4%)	22 (27%)	<0.001
Reoperation	32 (10.0%)	7 (3%)	25 (30%)	<0.001
Clavien Dindo:				<0.001
0	136 (42.4%)	136 (57.1%)	0 (0.00%)	
1	29 (9%)	29 (12.2%)	0 (0.00%)	
2	52 (16%)	48 (20%)	4 (5%)	
3	73 (23%)	16 (7%)	57 (69%)	
4	19 (6%)	6 (3%)	13 (16%)	
5	12 (4%)	3 (1%)	9 (11%)	
Total stay (days)	10.4 $\pm$ 11.3	7.34 $\pm$ 8.93	19.0 $\pm$ 13.0	<0.001
Mortality	13 (4%)	2 (1%)	11 (13%)	<0.001

SSI: surgical site infection; Me: median; SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; NNIS: National Nosocomial Infection Surveillance; ICU: Intensive care unit.

Note 1: Exploratory laparotomies were done in patients who were candidates for the procedure, but who were not candidates for surgery at the time of the operation due to progression of the disease.

Note 2: Four patients were excluded with diagnosis of liver metastases, one patient with cancer of the head of the pancreas and 15 patients with cholelithiasis because their samples were not viable for chromatographic analysis of vitamin D, with no presentations of SSI.

Regarding the multivariate analysis of the sample by vitamin D tertiles, a significant increase in the OR was observed in patients located in the third tertile (vitamin D > 43.3 nmol/L) compared to the lowest tertile (vitamin D < 25 nmol/L), which resulted in a significant decrease in the risk of SSI when the serum concentration of vitamin D increased (Fig. 1).

These differences were also confirmed in the model adjusted for sex, age, Charlson and type of surgery (urgent/scheduled) (Fig. 2).

Finally, by analyzing the sensitivity and specificity of vitamin D as a predictor for SSI, we found that values greater than or equal to 33.5 nmol/L reduced the risk of developing SSI by 50% (Fig. 3).

Discussion

SSI ranks second among the most prevalent nosocomial infections, and it is the most frequent in surgical patients.

Each SSI adds an average of 11 days to hospital stay and an average cost of €4,000.²²⁻²⁴

Our study registered 25.8% SSI, mainly organ/space infections (24.3%). This result is higher than the rates reported by Takahashi et al. and Moreno Elola-Olaso et al., who, in 2012, obtained post-hepatectomy infection rates of 4%-20% and an SSI incidence after liver resection of 2.1%-14.5%. However, the rates registered in our study were lower in terms of superficial and deep SSI, both of which were 1.2%.^{5,6}

In contrast, major hepatectomies recorded results similar to those described above, with an SSI incidence of 31.7%, while pancreaticoduodenectomies had almost 67% SSI.^{5,6}

These results, although high, should be analyzed in the context of our hospital, which is a referral center in our community for complex liver and pancreatic surgery.

As for cholecystectomies, the SSI rate was 1.5%, which is a lower result than other published reports if we take into account that the majority of infected patients underwent emergency and open surgery.^{5,7}

Table 2 – Surgical site infections data and agents by diagnostic group and totals.**LIVER AND BILE DUCTS**

Type of SSI	Total: 31
Superficial	1 (3%)
Deep	2 (7%)
Organ/space	28 (90%)
Isolated pathogens	N of isolations: 36
Other gram-negative	10 (28%)
<i>Enterococcus</i> spp.	6 (17%)
<i>Streptococcus</i> sp.	6 (17%)
<i>S.aureus</i> and other <i>Staphylococcus</i>	5 (14%)
<i>Klebsiella</i> spp.	4 (11%)
<i>E. coli</i>	3 (8%)
Other gram-positives	2 (6%)

PANCREAS

Type of SSI	Total: 34
Deep	1 (3%)
Organ/space	33 (97%)
Isolated pathogens	N of isolations: 67
<i>E. coli</i>	14 (21%)
Other gram-positives	14 (21%)
<i>Enterococcus</i> spp.	12 (18%)
Other gram-negatives	12 (18%)
<i>Klebsiella</i> spp.	8 (12%)
<i>Streptococcus</i> spp.	4 (6%)
<i>S.aureus</i> and other <i>staphylococcus</i>	2 (3%)
<i>Pseudomonas</i>	1 (2%)

GALLBLADDER AND DUODENUM

Type of SSI	Total: 20
Deep	2 (10%)
Organ/space	17 (90%)
Isolated pathogens	N isolations: 28
<i>E. coli</i>	7 (25%)
Other gram-negatives	7 (25%)
Other gram-positives	6 (21%)
<i>Enterococcus</i> spp.	3 (11%)
<i>Klebsiella</i> spp.	3 (11%)
<i>Pseudomonas</i>	1 (4%)
<i>S.aureus</i> and other <i>Staphylococcus</i>	1 (4%)

TOTAL DATA FOR SSI AND ISOLATED AGENTS

Type of SSI	Total: 85 ^a
Superficial	3 (4%)
Deep	3 (4%)
Organ/space	78 (92%)
Isolated pathogens	N isolations: 131
Other gram-negatives	29 (22.1%)
<i>E. coli</i>	24 (18.3%)
Other gram-positives	22 (16.8%)
<i>Enterococcus</i> spp.	21 (16%)
<i>Klebsiella</i> spp.	15 (11.5%)
<i>Streptococcus</i> spp.	10 (7.6%)
<i>S.aureus</i> and other <i>Staphylococcus</i>	8 (6.1%)
<i>Pseudomonas</i>	2 (1.5%)

SD: standard deviation; n: number of cases; Me: median; spp.: species.

The category “other gram-negatives” included: *Enterobacter* spp., *Haemophilus* spp., *Citrobacter* spp., etc; and “other gram-positives” included *Corynebacterium* spp., etc.

^a A total of 85 SSI were recorded; in one of the 84 patients, two types of infection were detected during follow-up (superficial and organ/space).

Table 3 – Univariate analysis of the surgical site infection regarding the reference variable.

	OR	P
Demographics		
Sex:		
Men	Ref.	Ref.
Women	0.47 [0.28;0.80]	0.005
Age (yrs)	1.02 [1.00;1.04]	0.034
Comorbidities		
Diabetes	0.79 [0.40;1.49]	0.473
Hypertension	1.06 [0.64;1.75]	0.815
COPD	4.12 [1.83;9.47]	0.001
Cardiopathy	1.84 [0.98;3.40]	0.059
Obesity	1.00 [0.56;1.76]	0.986
Malnutrition	3.10 [1.85;5.23]	<0.001
SSI	1.79 [0.58;5.06]	0.295
Neoplasms	2.04 [1.21;3.51]	0.007
Hospitalization last 18 months	2.61 [1.42;5.11]	0.002
ASA category:		
1	Ref.	Ref.
2	1.49 [0.64;3.93]	0.373
3–4	3.57 [1.54;9.45]	0.002
Charlson index:		
0	Ref.	Ref.
1	1.05 [0.16;6.80]	0.956
2	0.49 [0.02;4.69]	0.560
3	2.06 [0.52;10.8]	0.314
+4	2.76 [0.90;12.5]	0.080
Vitamin D data		
Serum concentration of vitamin D (nmol/L)	0.99 [0.97;1.00]	0.029
Categories of vitamin D		
<50 nmol/L	Ref.	Ref.
50–75 nmol/L	0.75 [0.35;1.49]	0.421
>75 nmol/L	0.59 [0.16;1.67]	0.337
Supplementation	1.48 [0.49;4.01]	0.462
Hospital stay and results		
Hospitalization in ICU (YES/NO)	5.41 [3.16;9.48]	<0.001
ICU stay (days)	1.16 [1.07;1.25]	<0.001
Readmission	8.05 [3.69;18.8]	<0.001
Reoperation	13.7 [5.91;36.3]	<0.001
Total stay (Days)	1.11 [1.07;1.14]	<0.001
Mortality	16.7 [4.28;120]	<0.001
Treatment		
Procedure:		
Segmentectomy and minor hepatectomy	Ref.	Ref.
Major hepatectomy	1.91 [0.79;4.60]	0.150
Pancreaticoduodenectomy and total pancreatectomy total	8.02 [3.34;20.4]	<0.001
Distal pancreatectomy	2.36 [0.54;9.18]	0.240
Cholecystectomy	0.72 [0.33;1.55]	0.390
Exploratory laparotomy	1.14 [0.36;3.23]	0.815
Hepaticojejunostomy	4.04 [0.64;25.7]	0.131
Procedure		
Type:		
Urgent	Ref.	Ref.
Scheduled	0.26 [0.11;0.64]	0.003
Approach:		
Open	Ref.	Ref.
Laparoscopic	0.23 [0.11;0.44]	<0.001
Duration	1.01 [1.01;1.01]	<0.001
NNIS index:		
0	Ref.	Ref.
1	3.14 [0.80;22.7]	0.109
2	10.4 [2.99;71.4]	<0.001

Table 3 (Continued)

	OR	P
3	29.4 [7.89;2.09]	<0.001
Transfusions	4.58 [2.47;8.58]	<0.001
Vasopressors	4.83 [2.39;9.95]	<0.001
Drain tubes	12.4 [5.32;37.0]	<0.001
Preoperative biliary stent	9.01 [4.04;21.8]	<0.001
Hospital stay and results		
Hospitalization in ICU	5.41 [3.16;9.48]	<0.001
ICU stay (days)	1.16 [1.07;1.25]	<0.001
Readmission	8.05 [3.69;18.8]	<0.001
Reoperation	13.7 [5.91;36.3]	<0.001
Total stay (days)	1.11 [1.07;1.14]	<0.001
Mortality	16.7 [4.28;120]	<0.001

Ref.: reference category; COPD: chronic obstructive pulmonary disease; CKF: chronic kidney failure; ASA: American Society of Anesthesiologists; NNIS: National Nosocomial Infection Surveillance; ICU: intensive care unit.

The biliary stent category includes all patients who had a prosthesis prior to surgery.

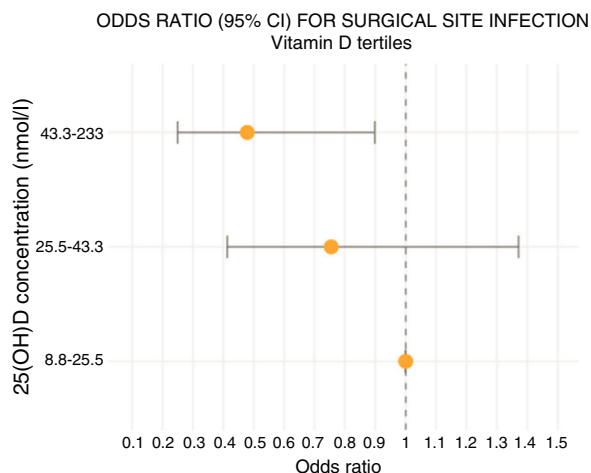


Fig. 1 – Multivariate analysis of the risk for surgical site infection, according to tertiles of vitamin D.

There was also a lower incidence of SSI in the laparoscopic approach compared to open surgery, which is in line with what has been published to date, despite the fact that 65% of the interventions were performed with this approach.⁴

As for vitamin D, the mean concentration was 38.3 ± 24.6 nmol/L, compatible with deficiency. To date, the only study carried out in serum concentrations of vitamin D in non-cardiac surgery patients is the publication by Turan et al. in 2014, which registered an average of 23.5 ng/ml (also within the range of deficiency⁹). However, there have been studies in bariatric patients, such as the Quaraishi S.A. et al. study,²⁵ which also obtained serum concentrations <30 ng/mL.

In 2012, Dima et al. published a bibliographic review on the potential effects of vitamin D in reducing nosocomial infections, which confirmed that vitamin D deficiency increased the predisposition towards *Staphylococcus aureus* infections and was associated with worse wound healing.^{21,26}

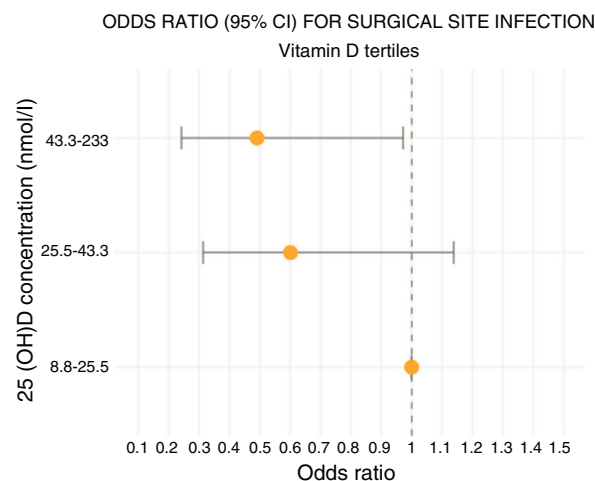


Fig. 2 – Multivariate analysis of surgical site infection occurrence by tertiles of vitamin D, adjusted for sex, age, Charlson index and type of surgery.

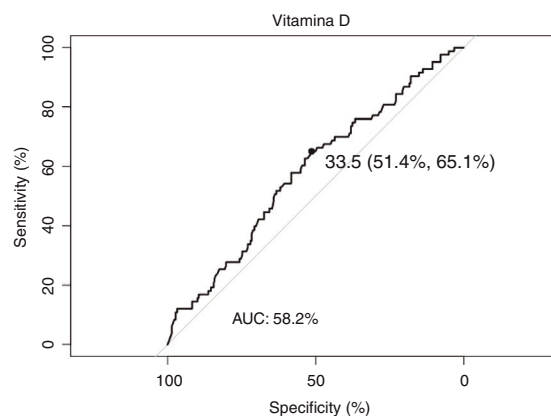


Fig. 3 – ROC curve of vitamin D plasma concentrations as a predictor for surgical site infection (SSI): values greater than or equal to 33.5 nmol/L reduce the risk of SSI by 50% with a sensitivity of 65.1% and a specificity of 51.4%. AUC: area under the curve.

According to serum concentrations of vitamin D, other studies have verified that there are differences in the results obtained in patients infected by certain microorganisms, such as *Clostridium difficile*, *S. aureus*, MRSA and *Pseudomonas aeruginosa*. Infected patients present hospital stays that are 4 times longer, at an increased cost of nearly five-fold.^{26,27}

Regarding the microorganisms isolated in SSI, Muñoz et al. conducted a study in 2011 in patients with digestive tract procedures, and they observed a predominance of gram-negative bacilli of digestive origin, together with gram-positive streptococci, enterococci and staphylococci. The most frequently isolated microorganisms were: *Escherichia coli* (28%), *Enterococcus* spp. (15%), *Streptococcus* spp. (8%), *Pseudomonas aeruginosa* (7%) and *Staphylococcus aureus* (5%).²⁸

In our sample, we also verified a significant percentage of gram-negative infections of digestive origin (22%) and similar isolation rates for *Enterococcus* spp., *Pseudomonas* spp. and *S. aureus*, but fewer isolated *E. coli* (18%) (Table 2).

To date, no study of this type has been carried out to analyze the relationship between SSI and serum vitamin D concentrations in hepatobiliary surgery. Our study population was found to have levels similar to previous publications,^{9,25,26,29} confirming that protein malnutrition and prolonged surgical time were the main risk factors.⁶

We have verified the existence of significant differences in terms of SSI when comparing patients in the lower and upper tertiles, and there was a significant decrease in SSI risk of 50% with concentrations of 33.5 nmol/L or more.

As limitations of our study, it should be noted that we have tried to eliminate the possible confounding factors with statistical adjustment of the multivariate analysis and the study of multiple demographic variables. However, we are aware of other confounding factors that may have gone unnoticed. Furthermore, the sample does not have a sufficient size to draw conclusions by diagnostic group regarding SSI and vitamin D, which is a reason for future studies with a larger sample size.

The results of our study suggest a correlation between serum vitamin D concentration and surgical SSI in hepatobiliary surgery, which justifies future prospective studies to assess the possible benefits of optimizing vitamin D before surgery and the influence of postoperative supplementation.

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Conflict of interests

The authors have no conflict of interests to declare.

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