

Antibiotic-loaded bone cement is associated with a reduction of the risk of revision of total knee arthroplasty: Analysis of the Catalan Arthroplasty Register

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Abstract

Purpose: The purpose of this study was to analyse the impact on peri-prosthetic joint infection (PJI) rate and prosthetic survival using antibiotic-loaded bone cement (ALBC) versus plain cement during total knee arthroplasty (TKA).

Methods: A retrospective cohort study was conducted. The main data source was the Catalan Arthroplasty Register (RACat). TKAs with surgery date between 1 January 2011 and 31 December 2020 were analysed and followed up until 31 December 2023. The main variable of interest was the type of cement (ALBC vs. plain cement), and several endpoints (septic revision, aseptic revision, and all-cause revision) were considered. The analysed outcomes were revision rates, survival rates and risk factors' hazard ratios (HR).

Results: A total of 22,781 TKAs were analysed, 13,125 (57.6%) of them with plain cement and 9656 (42.4%) with ALBC. The septic revision rate was lower in the ALBC group after 3 months of follow-up (0.52% vs. 0.78%, p value = 0.04). Prosthetic survival with respect to the aseptic revision endpoint was also higher for the ALBC group during the whole follow-up period (~158 months). Regarding risk factors for infection, ALBC showed a protective effect, HR: 0.53 (0.44, 0.63), while sex (being male) and the analysed comorbidities increased the risk.

Conclusions: ALBC is associated with a reduction in both the septic revision and the aseptic revision rate after TKA, and thus with higher prosthetic survival.

Level of Evidence: Level III, Therapeutic, retrospective.

KEYWORDS

antibiotic-loaded bone cement, peri-prosthetic joint infection, plain cement, total knee arthroplasty

Abbreviations: ALBC, antibiotic-loaded bone cement; BMSD, basic minimum set of data; CatSalut, Catalan health service; CPHM, Cox's proportional hazards model; ICS, Catalan institute of health; PJI, peri-prosthetic joint infection; RACat, Catalan arthroplasty register; TKA, total knee arthroplasty; VINCat, Catalan nosocomial infection surveillance programme.

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INTRODUCTION

Peri-prosthetic joint infection (PJI) is a major complication of total knee arthroplasty (TKA), which happens between 1% and 2% of the cases [10]. Patients who are affected by this complication usually need revision surgery, which has a big negative impact on the quality of life and leads to decreased patient satisfaction [11]. The last decades have witnessed many contributions and improvements aimed at reducing the rate of PJI. Some examples are the use of prophylactic antibiotics, improvements in orthopaedic theatres and modifications in pre-operative patient preparation [28]. In the case of total hip arthroplasty, the usage of antibiotic-loaded bone cement (ALBC) during primary arthroplasty has also been shown to decrease the rate of PJI [9, 14]. However, in the case of TKA, the evidence of the benefit of that strategy is inconclusive [21, 22]. Downsides such as the possibility of altering the mechanical properties of the cement, the generation of antibiotic microbial resistance or the increasing cost [7, 15, 18] cause a lack of consensus about this intervention across countries, and there is substantial variability in the findings reported by studies carried out in different countries or regions [21]. Places like the United Kingdom or the Scandinavian countries use ALBC in primary TKA in more than 90% of cases, but this percentage is much lower in places like the United States, Spain or Russia [30]. Furthermore, patients' preoperative characteristics can also be associated with the risk of developing PJI. Gender, age, previous surgeries and comorbidities, such as diabetes, obesity or inflammatory diseases could increase the probability of septic complications [26, 35].

The objective of this study was to analyse the data of the Catalan arthroplasty registry, the largest analysed registry of southern Europe, with the hypothesis that ALBC would not be associated with reductions in septic nor aseptic revision rates. It was also a secondary goal of the study to assess the impact of other risk factors, such as the patient's gender, age, comorbidities, and so forth.

METHODS

A retrospective cohort study was carried out, using data from the Catalan Arthroplasty Register (RACat), the Catalan nosocomial infection surveillance programme (VINCat), the Basic Minimum Set of Data (BMSD) of hospital discharges and databases of primary care. All data sources were managed by the Catalan health service (CatSalut) and the Catalan Institute of Health (ICS). The main source of data was RACat [2]. This regional, population-

based registry gathers information about knee and hip arthroplasties. It started its activity in 2005, and was a voluntary registry until 2015, when it became mandatory. It contains information from 51 out of the 56 public hospitals of Catalonia that perform TKAs under the coverage of CatSalut. VINCat contains information about hospital care-related infections, is a voluntary registry and receives information from all the major hospitals of Catalonia. The BMSD of hospital discharges and the databases of primary care contain information about hospital activity and primary care assistance, such as diagnoses and procedures. They are mandatory registries, and thus they are considered the *golden standard* of the database.

The starting point was the information on all knee arthroplasties contained in RACat with surgery dates between 1 January 2011 and 31 December 2020. The follow-up was until 31 December 2023. Partially cemented arthroplasties and uni-compartment arthroplasties were excluded, keeping only fully cemented TKAs. In addition, TKAs coming from hospitals with a low percentage of reported procedures were excluded, to avoid introducing biases. To compute the percentage of reporting for each hospital, first, we linked the RACat and the BMSD, requiring an exact match for patient identifier, surgery type and date of surgery. Then, the percentage of reported procedures was computed as the fraction of procedures registered by RACat with respect to those registered by BMSD. The threshold was set at 80% (see the Supporting Information for a justification of this value). Finally, TKAs with wrong or incomplete information were filtered out. This process resulted in 22,781 TKAs for final analysis. Figure 1 shows the STROBE [8] flow diagram of this process.

The main variable of interest was the use of ALBC or plain cement during primary TKA. The main outcomes of interest were prosthetic survival and revision rate, and the considered event was the revision, that is, a surgery after the primary surgery where at least one component was revised (excluding the patellar component). Depending on the diagnostic of the revision, three endpoints were specified: septic revision (revision due to infection), aseptic revision (revision due to a cause other than infection) and all-cause revision. In the remainder of this text, we may use the terms *septic revision* or simply *infection* interchangeably. The preoperative characteristics, covariates or risk factors considered were patient's age, as a continuous variable in years; sex assigned at birth, as a dichotomous variable (woman or man); obesity, diabetes, rheumatoid arthritis and alcohol abuse, as dichotomous variables (yes or no); smoking status, as a categorical variable (smoker, nonsmoker, former smoker; missing values treated as nonsmoker); body

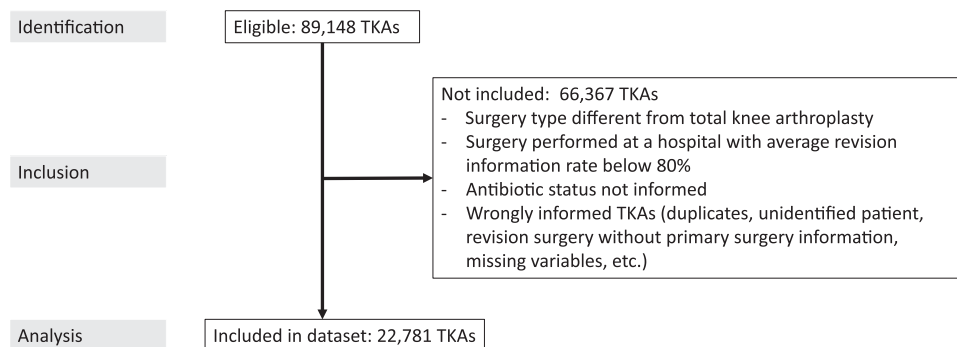


FIGURE 1 STROBE diagram of the study. The starting point consisted of 89,148 eligible TKAs. Finally 22,781 TKAs were included in the data set. TKA, total knee arthroplasty.

mass index (BMI) as a continuous variable in kg/m² (missing values imputed with the average stratified by age group); Charlson comorbidity index and Elixhauser index, as continuous variables; hospital category, as a categorical ordinal variable with five categories (between 1 and 5); primary surgery year, as a categorical ordinal variable (from 2011 to 2020); surgery duration, as a continuous variable in minutes (missing values assigned with the average stratified by the hospital). Note that the hospital category classifies hospitals regarding their size and specialization level, and it is a categorization established by CatSalut. Category 1 is for high-technology, reference hospitals, while Category 5 is for regional, basic hospitals. Alcohol abuse was defined as in the definition of the Elixhauser index [23].

We employed estimators and models that are widely used in survival analysis, such as the Kaplan–Meier estimator and the Cox proportional hazards models (see the Supporting Information for a justification of this choice). For the nonparametric models, estimators were computed for the two groups defined by the variable of interest, that is, ALBC or plain cement. Z-tests, *t* tests and Log-rank tests were used for determining whether observed differences between groups were statistically significant, with confidence value $\alpha = 0.05$.

The data were extracted, linked and analysed within the Data Analysis Program for Research and Innovation in Healthcare (PADRIS), managed by AQuAS, the Agency for Health Quality and Assessment of Catalonia.

National ethics committee approval with number PR186/19 and Advisory Committee of RACat approval were obtained for this study.

RESULTS

Table 1 presents a descriptive analysis of the most relevant preoperative characteristics of the study population, stratified by the variable of interest (plain

cement/ALBC). Overall, plain cement was used in 9656 (42.4%) cases and ALBC in 13,125 (57.6%) cases. In the ALBC group, gentamicin was used in 12703 (96.78%) cases, tobramycin in 410 (3.12%) cases and erythromycin in 12 (0.09%) cases. Small but statistically significant differences were found for sex and antibiotic usage (among females, 42.97% received plain cement and 57.03% ALBC, while among males, the percentages were 41.02% and 58.98%, respectively), and for age and antibiotic usage. No significant differences were found regarding the analysed comorbidities individually and antibiotic usage, although the small differences observed in the Charlson and Elixhauser indexes were statistically significant. Finally, larger differences were found for the variables of smoking status, surgery year and hospital category. The most significant one is the steady increase in ALBC usage over the years, going from 46.74% in 2011 to 84.16% in 2020 (of all surgeries in each year, respectively).

The follow-up period was 158 months (approximately 13 years). Figure 2 shows the Kaplan–Meier survival curves for three endpoints, septic revision (a), aseptic revision (b) and all-cause revision (c), for the whole duration of the follow-up period. The ALBC group showed higher survival values across study time for all endpoints (p value < 0.05 in all cases). The survival values (with 95% confidence intervals in brackets) at the end of the follow-up period were 95.2% (93.4%, 96.5%) for ALBC and 95.2% (94.3%, 96%) for plain cement, in the case of septic revision; 90.2% (86.7%, 92.9%) for ALBC and 85% (83.8%, 86.1%) for plain cement, in the case of aseptic revision; and 85.9% (82.3%, 88.8%) for ALBC and 81% (79.6%, 82.2%) for plain cement, in the case of all-cause revision.

Table 2 and Figure 3 show the results of infection rates and Kaplan–Meier survival curves for both ALBC and plain cement groups, for the endpoint of septic revision and shorter follow-up times (3, 6, 12 and 24 months, respectively). Uncensored data was used for this analysis, reducing the risk of bias of the

TABLE 1 Preoperative characteristics of the study population, stratified by the cement type.

Characteristic	Categories	Plain cement	ALBC	p Value
		<i>n</i> (%)		
Sex	Female	6843.0 (42.97%)	9081.0 (57.03%)	<0.01
	Male	2813.0 (41.02%)	4044.0 (58.98%)	
		mean (SD)		
Age (years)		72.24 (7.61)	71.94 (8.01)	<0.01
Hospital category	1	2246.0 (49.50%)	2291.0 (50.50%)	<0.01
	2	175.0 (4.20%)	3994.0 (95.80%)	
	3	3232.0 (48.56%)	3423.0 (51.44%)	
	4	3995.0 (56.32%)	3099.0 (43.68%)	
	5	8.0 (2.45%)	318.0 (97.55%)	
		mean (SD)		
Surgery duration		89.82 (14.40)	89.98 (21.21)	n.s.
Charlson index		0.41 (0.76)	0.46 (0.79)	<0.01
Elixhauser index		1.34 (1.18)	1.41 (1.20)	<0.01
		<i>n</i> (%)		
Obesity	No	8509.0 (42.49%)	11,518.0 (57.51%)	n.s.
	Yes	1147.0 (41.65%)	1607.0 (58.35%)	
Diabetes	No	8112.0 (42.68%)	10,893.0 (57.32%)	0.04
	Yes	1544.0 (40.89%)	2232.0 (59.11%)	
Rheumatoid arthritis	No	9460.0 (42.47%)	12,817.0 (57.53%)	n.s.
	Yes	196.0 (38.89%)	308.0 (61.11%)	
Alcohol abuse	No	9601.0 (42.43%)	13,025.0 (57.57%)	n.s.
	Yes	55.0 (35.48%)	100.0 (64.52%)	
Smoking status	Nonsmoker	7985.0 (43.37%)	10,426.0 (56.63%)	<0.01
	Smoker	555.0 (39.67%)	844.0 (60.33%)	
	Former smoker	1116.0 (37.56%)	1855.0 (62.44%)	
		mean (SD)		
Body mass index		31.82 (4.57)	31.76 (4.89)	n.s.

Abbreviation: ALBC, antibiotic-loaded bone cement.

Kaplan–Meier estimator. The infection rate was lower for the ALBC group in all cases with statistically significant differences (p value < 0.05 in all cases).

Figure 4 shows a boxplot of the hazard ratios (HR) of the different covariates and the variable of interest (ALBC/plain cement) for septic revision, obtained by fitting Cox's proportional hazards model. The associated numerical information can be found in Table 3. ALBC was associated with a protective effect over infection (HR: 0.53 (0.44, 0.63), p value < 0.01). Other covariates, such as alcohol abuse, rheumatoid arthritis, obesity, diabetes and surgery year, were associated with a higher rate of infection (although Diabetes was

not statistically significant by a small margin). Hospital category and sex showed a protective effect. Smoking status, BMI, surgery duration and age showed small or statistically not significant effects. Risk factor analysis for the endpoints of aseptic revision and all-cause revision can be found in the Supporting Information.

DISCUSSION

The most important finding of this study was that ALBC was associated with lower septic and aseptic revision rates after TKA, and thus with higher prosthetic

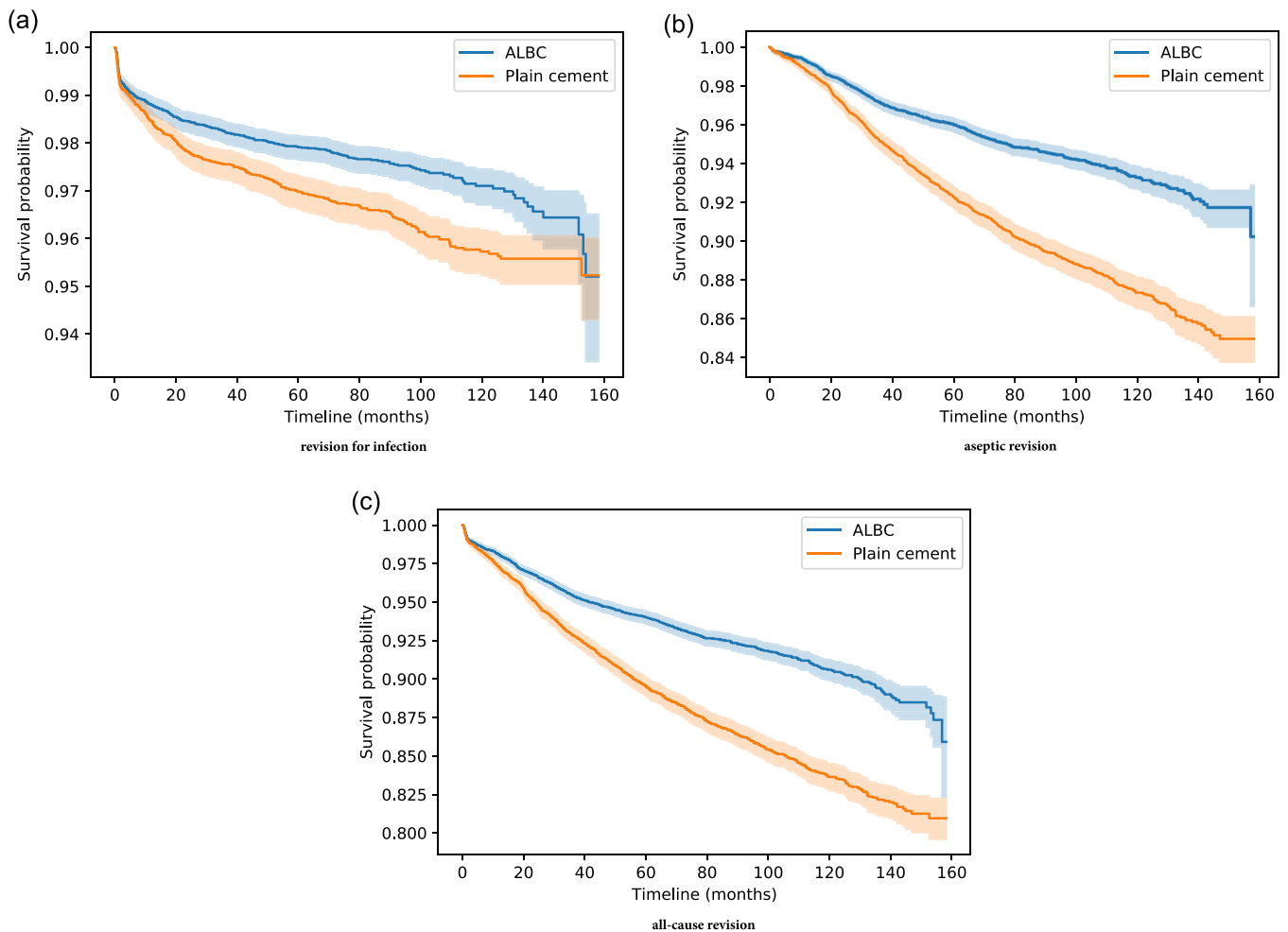


FIGURE 2 Kaplan–Meier curves for three endpoints: (a) revision for infection, (b) aseptic revision and (c) all-cause revision. Significant differences in survival rates are observed in all three cases, in favour of the ALBC group. ALBC, antibiotic-loaded bone cement.

TABLE 2 Infection rates for short follow-up times, stratified by the cement type.

Follow-up time	Cement type		p Value
	Plain cement %	ALBC %	
3 months	0.78	0.52	0.04
6 months	0.98	0.68	0.04
12 months	1.33	0.72	<0.01
24 months	1.79	0.84	<0.01

Abbreviation: ALBC, antibiotic-loaded bone cement.

survival, in the largest analysed TKA registry of southern Europe to date. The suggested mechanism for the protective effect of ALBC against infection is that the initial concentration of antibiotic released when performing the TKA would be enough to prevent bacterial biofilm formation [14, 17, 3].

The evidence of the benefits of using ALBC during TKA is inconclusive in the scientific literature, with some studies reaching conclusions in favour of it [16,

17], others against [27, 33] and others finding no differences [5, 13].

Our results align with those of the study with the largest sample size coming from a single database, the National Joint Registry from England and Wales [16]. In that work, the vast majority of analysed TKAs (93%) belonged to the ALBC group, and that circumstance also happened in other studies whose results are aligned with ours [17]. In the present work, nevertheless, the distribution between groups was more balanced: 57.6% in the ALBC group and 42.4% in the plain cement group.

Among the studies that found negative or no effect of ALBC, some performed the analysis in a sequential way [33], first doing a univariate analysis and then doing a multivariate analysis with factors that had achieved statistical significance in the first step. On the contrary, our analysis was carried out in a multivariate manner with all the variables in a single step. Some works may have suffered from confounding bias [28], as patients in the ALBC group had significantly higher values of risk factors, such as Diabetes Mellitus or ASA

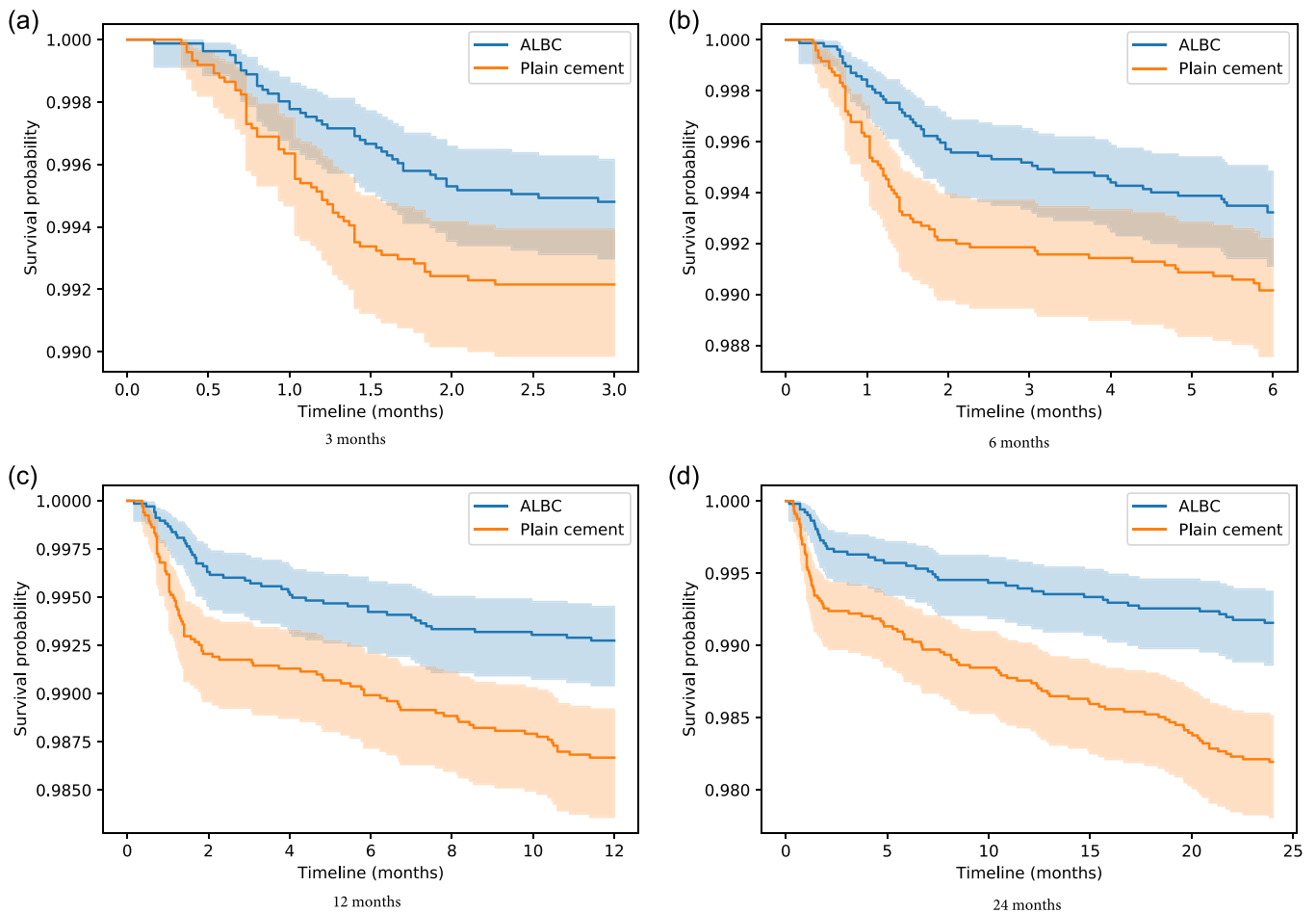


FIGURE 3 Kaplan-Meier survival curves for infection, for different follow-up times: (a) 3 months, (b) 6 months, (c) 12 months and (d) 24 months. Differences are observed for all four scenarios, which become larger with the follow-up time. ALBC, antibiotic-loaded bone cement.

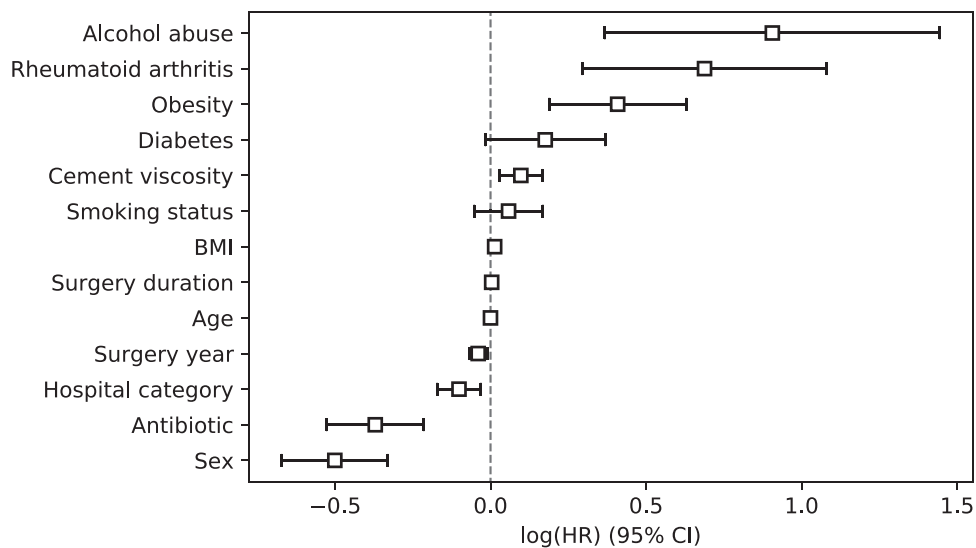


FIGURE 4 Boxplot of the hazard ratios of the Cox proportional hazards model with preoperative covariates in decreasing order.

TABLE 3 Cox proportional hazards model's results for endpoint infection.

		Hazard ratio	Event count 658	No event count 22,123	p Value
Antibiotic	Plain cement	ref	344	9312	<0.01
	ALBC	0.53 (0.44, 0.63)	314	12,811	
Sex	Male	Ref	270	6587	<0.01
	Female	0.61 (0.52, 0.73)	388	15,536	
Age		1.00 (0.99, 1.01)	71.54 (8.32)	72.08 (7.83)	n.s.
Hospital category	1	1.11 (1.19,1.03)	129	4408	0.01
	2	Ref	140	4029	
	3	1.22 (1.41,1.06)	208	6447	
	4	0.90 (0.84,0.97)	173	6921	
	5	0.82 (0.71,0.94)	8	318	
Surgery duration		1.00 (1.00, 1.01)	92.71 (31.74)	89.83 (18.09)	<0.01
Alcohol abuse	No	ref	644	21,982	<0.01
	Yes	2.31 (1.35, 3.96)	14	141	
Diabetes	No	Ref	525	18,480	<0.01
	Yes	1.25 (1.03, 1.51)	133	3643	
Obesity	No	ref	541	19,486	<0.01
	Yes	1.61 (1.29, 2.00)	117	2637	
Rheumatoid arthritis	No	Ref	632	21,645	<0.01
	Yes	1.92 (1.29, 2.84)	26	478	
Smoking status	Nonsmoker	ref	499	17,912	ref
	Smoker	1.13 (0.83, 1.54)	51	1348	n.s.
	Former smoker	1.10 (0.88, 1.38)	108	2863	n.s.
BMI		1.01 (0.97, 1.03)	32.26 (5.16)	31.77 (4.74)	n.s.

Abbreviations: ALBC, antibiotic-loaded bone cement; BMI, body mass index.

grade. This was not the case in our registry. Finally, some other studies used antibiotics, such as erythromycin and colistin [13], which are less routinely used than gentamicin, the predominant antibiotic in our database.

The meta-analyses that have been published on the topic to date have shown, in general, no statistically significant differences in infection rates between groups [18, 22, 23]. Nevertheless, in the largest and most recent multiregistry meta-analysis found in the literature [23], four out of nine registries showed results aligned with ours' (i.e., in favour of ALBC), and two of them achieved statistical significance. It is worth mentioning that such meta-analysis considered the underrepresentation of some regions of the world a potential limitation for the generalizability of its findings, and yet the southern European region was rather underrepresented (both in that study and in the literature in general). In another meta-analysis [22] no

statistically significant differences between groups were found, although it is interesting to note that the two largest studies included did report them, both in favour of ALBC. Most of the largest studies analysed in that meta-analysis have already been discussed in this section.

A secondary finding in our study was that the ALBC group also showed lower aseptic revision rates and higher prosthetic survival than the plain cement group. These results were aligned with the findings of several works in the literature [4, 5, 16], with the plausible explanation that ALBC could have acted as a protective factor against subclinical infections misclassified as aseptic loosening. Other studies found no effect or a negative one, suggesting that it could be caused by the worsening of the mechanical properties of the prostheses due to the ALBC. The evidence for that mechanism was found mostly in vitro [20, 25], and we did not observe it in our data. Some other works indicate that

wrongly classified subclinical infections could bias the results of aseptic revision rates [24, 6].

Previous works have also analysed the associated risk of preoperative characteristics with prosthetic survival [17, 29, 31, 35]. In our data, sex (being male) was found to be a risk factor for infection after TKA, in line with other works [13, 19, 26]. Alcohol abuse, diabetes, obesity and rheumatoid arthritis were also risk factors for infection. Regarding obesity, a study indicated that local adiposity could be a better predictor for infection than the BMI [12], but our registry did not contain that information. Being a smoker or a former smoker was also associated with a higher risk of infection, although this variable did not achieve statistical significance. The results on all these risk factors were in line with those of the largest meta-analysis carried out to date [32], except for the fact that we did not find age to be a protective factor.

Our study has limitations. First, RACat data completeness can vary for each hospital. We tried to overcome this by analysing TKAs performed in hospitals that had at least an 80% of prosthetic revision reporting rate, but the limitation was still present. Second, to identify PJI, septic revision diagnostic categories of RACat were used. Infections that were not treated surgically, whether superficial or deep, were not identified by this method. Nevertheless, this limitation is shared with other studies, making results comparable in principle. Finally, inputted values for the missing values of some of the available confounders, or the effect of other, unexplored confounders (such as surgical time, individual surgeons, individual hospitals or others) could have introduced bias in the results.

Overall, the combination of our results in favour of ALBC with some others indicating that it is cost-effective [1] and that its use is not associated with bacterial resistance [34] brings evidence in favour of its routine use. We are aware that the most recent meta-analyses do not find significant benefits, and we consider that larger pragmatic trials are required.

CONCLUSIONS

In our study, the use of ALBC was associated with a lower rate of septic and aseptic revision, and thus with higher prosthetic survival, suggesting that its routine use was beneficial. In addition, the main risk factors for PJI were sex (being male), obesity, diabetes, rheumatoid arthritis and alcohol abuse.

AUTHOR CONTRIBUTIONS

Sergi Gil-Gonzalez: Conceptualization; methodology; formal analysis and investigation; writing—review and editing. **Borja Velasco-Regúlez:** Methodology; formal analysis and investigation; writing—original draft preparation. **Jesus Cerquides:** Methodology; formal

analysis and investigation; writing—review and editing; funding acquisition; supervision. **Pedro Hinarejos:** Conceptualization; supervision. **Joan Carles Monllau:** Conceptualization; supervision. **Xavier Pelfort:** Conceptualization; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data employed for this study was individual patient pseudo-anonymized data, which was obtained under the coverage of the Data Analysis Program for Research and Innovation in Healthcare (PADRIS), managed by AQuAS, the Agency for Health Quality and Assessment of Catalonia. This data cannot be made available publicly.

ETHICS STATEMENT

National ethics committee approval with number PR186/19 and institutional review board were obtained for this study. The related documentation can be made available upon request.

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