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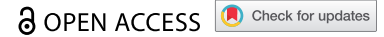


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ORIGINAL RESEARCH



Is the survival of patients treated with ipilimumab affected by antibiotics? An analysis of 1585 patients from the French National hospital discharge summary database (PMSI)

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ABSTRACT

Background: The gut microbiota has a key role in the regulation of the immune system. Disruption of the gut microbiota's composition by antibiotics might significantly affect the efficacy of immune checkpoint inhibitors. In a study of patients treated with ipilimumab, we sought to assess the relationship between overall survival and in-hospital antibiotic administration.

Methods: Patients having been treated with ipilimumab between January 2012 and November 2014 were selected from the French National Hospital Discharge Summary Database. Exposure to antibiotics was defined as the presence of a hospital stay with a documented systemic bacterial infection in the 2 months before or the month after initiation of the patient's first ever course of ipilimumab. The primary outcome was overall survival.

Results: We studied 43,124 hospital stays involving 1585 patients from 97 centers. All patients had received ipilimumab monotherapy for advanced melanoma. Overall, 117 of the 1585 patients (7.4%) were documented as having received systemic antibiotic therapy in hospital during the defined exposure period. The median overall survival time was shorter in patients with infection (6.3 months, vs. 15.4 months in patients without an infection; hazard ratio (HR) = 1.88, 95% confidence interval [1.46; 2.43], $p = 10^{-6}$). In a multivariate analysis adjusted for covariates, infection was still significantly associated with overall survival (HR = 1.68, [1.30; 2.18], $p = 10^{-5}$).

Conclusions: In patients treated with ipilimumab for advanced melanoma, infection, and antibiotic administration in hospital at around the time of the patient's first ever course of ipilimumab appears to be associated with significantly lower clinical benefit.

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Introduction

Since their clinical introduction in 2010, immune checkpoint inhibitors (ICIs) have revolutionized cancer management. This drug class has become the fifth pillar of cancer treatment, along with surgery, radiotherapy, chemotherapy, and targeted therapy.¹ In France, the first marketing authorization for an ICI was granted in July 2011, for the monoclonal antibody ipilimumab as a second-line treatment for advanced (unresectable or metastatic) melanoma.² The drug was initially prescribed under a temporary authorization for use, and reimbursement under the national social security system was obtained in April 2012. In October 2013, ipilimumab's marketing authorization was extended to first-line treatment. The marketing authorization and reimbursement covered up to four courses of ipilimumab monotherapy, i.e. a total of 3 months of treatment. Up until 2014, melanoma was the only approved indication for ICIs in France.² Ipilimumab binds to CTLA4, which has a major role in regulating T cell function.³ The antibody lifts constraints on preexisting

anticancer T cell responses and might also trigger a new immune response.⁴

Antibiotics are widely used in oncology. Treatment with antibiotics alters the gut microbiota qualitatively and quantitatively.⁵ The exact nature of these changes depends on many factors, including the class of antibiotic,^{5,6} the duration of administration,⁶ and the dose administered.⁷ Furthermore, the gut microbiota have a key role in regulating the immune balance.⁸⁻¹⁰ It has therefore been hypothesized that by disturbing the gut microbiota, antibiotics may be responsible (at least in part) for the lack of an effective response to ICIs observed in some patients.¹¹⁻¹³

This hypothesis was first explored in several preclinical studies.¹¹⁻¹³ From 2017 onwards, several retrospective and prospective clinical studies then evaluated the association between antibiotics and the efficacy of immunotherapy.¹⁴⁻³⁰ All of these studies showed significantly worse progression-free and/or overall survival in the group of patients exposed to antibiotics. The relative decrease in median overall survival ranged from 3.8 to 16.7 months.¹⁶ The only study that did

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not evidence lower efficacy had a small study population ($n = 74$ patients).²³ Nevertheless, the retrospective nature of these studies and their small sample sizes limit the robustness of the conclusions; additional data on this issue are required.

Routine clinical practice generates huge amounts of data.³¹ This is notably the case for the French National Hospital Discharge Summary Database (PMSI), whose data can be reused for medical research.^{32–34} Some drugs of interest have a specific reimbursement process that requires exhaustive reporting in the PMSI database; this is the case for certain monoclonal antibodies in the PMSI database,³⁵ and especially ipilimumab.

The primary objective of the present study was to determine whether the overall survival of patients treated with ipilimumab is influenced by antibiotics. To this end, we performed a data reuse analysis of the PMSI database and assessed the association between the overall survival of patients treated with ipilimumab for advanced melanoma on one hand and the presence of hospital stays with an infection and in-hospital antibiotic administration on the other.

Material & methods

Study design and data source

We carried out a population-based, retrospective cohort study using data extracted from the PMSI database, which contains standardized discharge reports from all patients discharged from for-profit or nonprofit hospitals in France. Each discharge report provides administrative and demographic data, and information on diagnoses, diagnostic procedures, therapeutic procedures, and some specific administered drugs. Diagnoses are encoded as primary or secondary diagnoses using the French version of the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10).³⁶ Therapeutic and diagnostic procedures are recorded according to the French “common classification of medical procedures” terminology (CCAM).³⁷ Administered drugs (when recorded) are encoded with the French common dispensing unit (CDU) terminology.³⁸ Discharge reports are mandatory and serve as the basis for the funding of both for-profit and nonprofit hospitals. This database also includes a unique, anonymous patient identifier that enables one to link together all a given patient’s inpatient stays – even when the patient has been admitted to several different healthcare facilities.

This study had been conducted in compliance with the French Regulation (MR004), and was approved by the French data protection agency (Commission nationale de l’informatique et des libertés (Paris, France), approval number: DE-2017-277). All data were anonymized. According to French Regulation, obtaining written consent does not apply to research work using such a database.

Study population

We searched the PMSI database for hospital discharges of adult (over-18) patients who being admitted for a first course of ipilimumab (hereafter denoted as “C1”) between January 1st,

2012, and November 30th, 2014 (CDU codes: 9374067 and 9374050). It should be noted that at this time, ipilimumab was only authorized as a monotherapy for malignant melanoma. The selected patients were included at C1 and followed up until December 2014. We also extracted data on all hospital stays by the selected patients between January 1st, 2008, and C1.

Study variables

The following items of information were extracted for each patient: age, sex, ICD-10 diagnoses, CCAM procedures, CDU drug codes, and inpatient stays (admission and discharge dates). Using feature extraction, the patients were classified according to their ICD-10 diagnosis.³⁴

The proxy for systemic in-hospital exposure to antibiotics was defined as any hospital admission with a diagnosis of a systemic bacterial infection (see the list of codes in the supplementary material: [Appendix 1](#)) beginning in the 2 months before or in the month following the study inclusion date (i.e. C1). We defined two study groups: the “infection” group comprised all patients with at least one hospital admission with a systemic bacterial infection, and the “no infection” group comprised all other selected patients.

The study outcome was death from any cause. The primary endpoint was overall survival, defined as the time interval between C1 and the date of death from any cause. For non-deceased patients, data were censored at the end of the exhaustive follow-up period (December 2014).

The study consisted of three parts. Firstly, our main analysis took account of the period of possible antibiotic exposure most commonly used in the literature¹⁶ (i.e. the 2 months before C1 and in the month following C1). Secondly, we performed a sensitivity analysis that considered only exposure during the 2 months before C1. Lastly, we performed a negative control analysis by considering antibiotic exposure far from C1 (i.e. between 12 and 2 months before C1).

Statistical analysis

Continuous variables were described as the mean (standard deviation (SD)) or the median [interquartile range (IQR)], as appropriate. Categorical variables were described as the frequency (percentage). To compare the characteristics of the “infection” vs. “no infection” groups, we used the chi-squared test or Fisher’s exact tests for categorical variables and Welch’s two-sample T-test for quantitative variables.

The Kaplan-Meier method was used to estimate survival rates overall and in subgroups. The hazard ratio (HR) for death associated with infection was estimated using Cox models – first in a bivariate analysis, and then in a multivariate analysis adjusted for possible confounders. The following covariates (all available in the PMSI) were considered: age (18–39 vs. 40–65 vs. >65 years), sex, severe malnutrition at C1, brain metastases at or before C1, previous chemotherapy, and the cumulative length of hospital stays before C1 (<50 days vs. ≥50 days, taking into account all possible stays in the period 2008–2014). The initial multivariate model included all covariates associated with a p -value <0.20 in bivariate analyses. The

final multivariate model included only covariates associated with p -value <0.05 .

All estimates are quoted with their 95% confidence intervals [95%CI]. All tests were two-sided, and the threshold for statistical significance was set to $p < .05$.

There were no missing data. All statistical analyses were performed using R software.³⁹

Results

Patient population and characteristics

We identified 1585 adult patients having received ipilimumab monotherapy for advanced melanoma between January 1st, 2012, and November 30th, 2014, and extracted a total of 43,124 hospital stays in 97 different French hospitals from 2008 to 2014. C1 occurred in 2012 for 121 patients (7.6%), in 2013 for 469 patients (29.6%), and in 2014 for 995 patients (62.8%).

Overall, 117 (7.4%) patients were considered to have received antibiotics in hospital during the main exposure period (i.e. the 2 months before C1 and the month following C1). It should be noted that a given patient could have several infections during the period of exposure. The following infection sites were recorded: the skin ($n = 35$, 21.6%), the respiratory tract ($n = 34$, 20.4%), the digestive system ($n = 23$, 14.4%), the urinary tract ($n = 18$, 11.1%), bones/joints ($n = 12$, 7.4%), catheters ($n = 10$, 6.2%), the cardiac valves ($n = 6$, 3.7%), the upper respiratory tract ($n = 4$, 2.5%), the brain or the meninges ($n = 2$, 1.2%), or an unknown site ($n = 18$, 11.1%). Inpatient stays with infection accounted for 42% of all stays during the defined exposure period.

The mean number of courses of ipilimumab was lower in patients with an infection than in patients without an infection (2.7 vs. 3.6, $p = 10^{-5}$).

Baseline patient characteristics are described in Table 1.

The main analysis

According to the reverse Kaplan-Meier method, the median follow-up time was 8.7 months. 592 deaths were observed. The median [IQR] overall survival rate was 71% [69;73] at 6 months and 55% [52;58] at 12 months. As illustrated by the Kaplan-Meier curves (Figure 1), overall survival from C1 was

significantly lower in patients with an infection than in patients without an infection (HR = 1.88 [1.46; 2.43], $p = 10^{-6}$), leading to median overall survival times of 6.3 and 15.4 months, respectively.

The estimated effect size associated with infection was stable and statistically significant in a multivariate analysis, with an HR of 1.68 ([1.30; 2.18], $p = 10^{-5}$) after adjustment for severe malnutrition and brain metastases (Table 2).

The sensitivity analysis

In the sensitivity analysis (considering the 2 months before C1 as the exposure period), 71 of the 1585 (4.5%) patients were considered to have received antibiotics in hospital.

The HR (1.65, [1.19; 2.28], $p = .0023$) was very similar to that obtained in the main analysis. The median overall survival time was 8 months in patients with an infection and 15.1 months in patients without an infection. The Kaplan-Meier estimates are given in Appendix 2.

The negative control analysis

When considering an exposure period between 12 and 2 months before C1, 147 of the 1585 (9.3%) patients had received antibiotics in hospital. The median overall survival was similar in the two groups: 15.4 months in patients with an infection and 14.5 months in patients without an infection (HR = 0.99, [0.75; 1.30], $p = .94$). The Kaplan-Meier estimates are given in Appendix 3.

Discussion

In the present study of patients treated with ipilimumab for advanced melanoma, we examined the association between the presence of hospital stays with bacterial infection and in-hospital antibiotic administration on one hand and overall survival on the other. Our main finding is that antibiotic exposure in the 2 months before C1 and in the month following C1 was significantly associated with a decrease in overall survival (unadjusted HR = 1.88; adjusted-HR = 1.68). The median survival time was 6.3 months in patients with an infection and 15.4 months in patients without an infection. The same association was found when the exposure period was

Table 1. Patient population and baseline characteristics.

Characteristics	Overall population (n = 1585)	No infection (n = 1468)	Infection (n = 117)	p-value
Age at C1 in years, mean (SD)	62.2 (14.6)	62.3 (14.6)	61.1 (13.9)	.39
Males, n (%)	876 (55.3%)	808 (55.0%)	68 (58.1%)	.58
Severe malnutrition at C1, n (%)	34 (2.15%)	28 (1.91%)	6 (5.13%)	.035
Brain metastases at C1 or before C1, n (%)	277 (17.5%)	244 (16.6%)	33 (28.2%)	.002
Chemonaive, n (%)	663 (41.8%)	620 (42.2%)	43 (36.8%)	.29
Total number of previous courses of chemotherapy, median [IQR]	2 [0;7]	2 [0;7]	2 [0;8]	.53
Number of courses of chemotherapy during the year before C1, median [IQR]	1 [0;5]	1 [0;5]	2 [0;6]	.39
Cumulative length of hospital stays before C1 ≥ 50 days ¹ , n (%)	530 (33.4%)	477 (33.4%)	53 (45.3%)	.006

C1: the start date of the first course of ipilimumab

SD: standard deviation

IQR: interquartile range

¹Number of patients who were hospitalized for a total of ≥ 50 days before C1, taking into account all possible stays in the period 2008–2014.

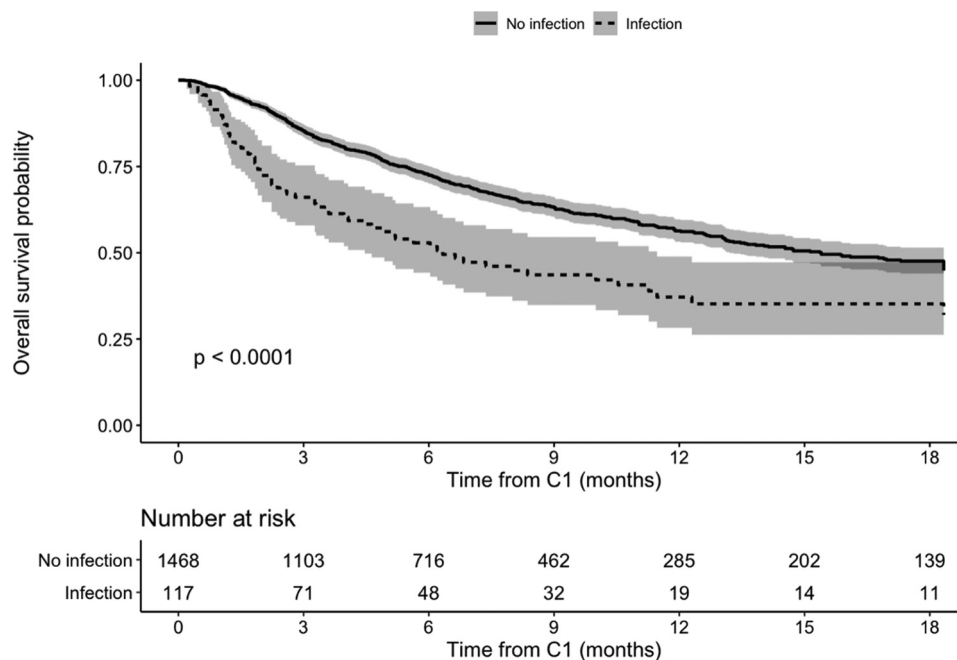


Figure 1. Overall survival according to the Kaplan-Meier method, main analysis (p -value from the Cox bivariate model).

Table 2. The Cox model.

	Bivariate HR [95% CI] and p -value	Multivariate HR: full model [95% CI] and p -value	Multivariate HR: final model [95% CI] and p -value
Age at C1, in years (ref. = 18–39)			
40–64	1.08 [0.80; 1.44] $p = .63$	1.06 [0.80; 1.43] $p = .70$	
65–95	0.71 [0.53; 0.96] $p = .03$	0.76 [0.56; 1.03] $p = .08$	
Male sex	1.11 [0.95; 1.31] $p = .20$		
Infection group	1.88 [1.46; 2.43] $p = 10^{-6}$	1.66 [1.28; 2.15] $p = 10^{-4}$	1.68 [1.30; 2.18] $p = 10^{-5}$
Severe malnutrition	4.85 [3.27; 7.20] $p = 10^{-15}$	4.18 [2.81; 6.23] $p = 10^{-12}$	4.39 [2.96; 6.53] $p = 10^{-13}$
Brain metastases	2.00 [1.66; 2.40] $p = 10^{-13}$	1.79 [1.48; 2.16] $p = 10^{-9}$	1.89 [1.57; 2.27] $p = 10^{-11}$
Previous chemotherapy	1.20 [1.00; 1.43] $p = .04$	1.08 [0.90; 1.30] $p = .41$	
Cumulative length of hospital stays before C1 \geq 50 days	1.12 [0.95; 1.33] $p = .17$	1.02 [0.86; 1.21] $p = .86$	

restricted to the 2 months before C1. We did not find any association when considering antibiotic exposure far from ICI treatment (i.e. between 12 and 2 months before C1).

By reducing the exposure period to the 2 months prior to C1, the sensitivity analysis reduced several sources of bias in antibiotic exposure: (i) administration related to a deterioration in general condition (e.g. the absence of early effectiveness of immunotherapy, unrelated to the infection and the administration of antibiotics), and (ii) administration for

the treatment of adverse events associated with ipilimumab (e.g. colitis).

The purpose of the negative control analysis was to determine whether an infection long before C1 had any impact on survival. The lack of an association in the negative control analysis reinforced the hypothesis whereby recent or concomitant administration of antibiotics could disrupt the effectiveness of ICI by altering the gut microbiota.

Our present results are in agreement with most studies of the association between infections and ipilimumab. These were also retrospective studies. Elkrief et al. found shorter survival times in their group of melanoma patients with an infection during the month before the first course of ipilimumab ($n = 10/74$, 13.5%): the median progression-free survival was significantly shorter (2.4 months, vs 7.3 months in patients without an infection, HR = 0.28, [0.10; 0.76], $p = .01$), as was the median overall survival time (10.7 vs. 18.3 months, respectively; HR = 0.52, [0.21; 1.32], $p = .17$).¹⁷ In Tinsley et al.'s study, which included a majority of melanomas (61.5%), the administration of antibiotics during the period 2 weeks before or 6 weeks after ipilimumab initiation was associated with a significantly shorter median progression-free survival time (3.1 months, vs. 6.3 months patients without antibiotics; HR = 1.56, $p = .003$) and median overall survival time (10.4 vs. 21.7 months, respectively; HR = 1.70, $p = .002$).²⁸ Most recently, Mohiuddin et al. analyzed 568 patients with stage III or IV melanoma. In a multivariate analysis of patients with stage IV melanoma, overall survival was significantly worse in the antibiotic-exposed group than in the non-exposed group (HR = 1.81, [1.27; 2.57]).⁴⁰

Our study had several strengths. Firstly, to the best of our knowledge, it constituted the largest yet study (in terms of the sample size) to have addressed this issue. Secondly, the study population was highly representative, with exhaustive data collection. For example, our data for 2014 covered more than

99% of patients newly treated with ipilimumab, as identified by French National Cancer Institute (*Institut National du Cancer*).² Thirdly, the present study is the first (to the best of our knowledge) to have used a national database to explore this issue. Lastly, this was a real-life cohort study.

However, the study also had some limitations. Firstly, we did not have access to primary data on the antibiotic administration as per or to data on outpatients. This may have led us to consider some “exposed” patients as “non-exposed” patients, i.e. classification bias. Secondly, we did not have access to detailed data on the cancer subtype (e.g. BRAF mutation status) or antibiotic exposure (e.g. drug class, combination, or not, route, duration, and dose). Consequently, our multivariate model contained a small number of covariates and therefore only partially captured the indications for antibiotics. This, even though the clinical context in which antibiotics are administered must be kept in mind: advanced disease is more likely to be complicated by infections (i.e. an indication bias).²⁴ Lastly, it should be noted that the data in this work concerned exclusively ipilimumab, and that ipilimumab is no longer the standard monotherapy for advanced melanoma. Indeed, the data available for this study only extended to December 31, 2014. This is due to the delay between the collection of the data in the PMSI database and the availability of these data for their analysis. However, this work will constitute the background and the proof-of-concept for the exploitation of the most recent PMSI data. These data will include other types of ICIs (particularly anti-PD1) and other cancer sites (including lung, kidney, and bladder).

As in previously published studies, the effect of antibiotics *per se* cannot be disentangled from that of the infection. Resolving this issue is both methodologically and ethically challenging.

Our study’s prime conclusion is that the administration of antibiotics close to (and especially just before) the first course of ipilimumab may explain (at least in part) the non-response observed in some cancer patients. The question is then whether these patients should receive another class of therapeutic agent. Our second conclusion is that it is important to prescribe antibiotics sparingly and to limit their use to strictly necessary situations. However, for some patients, antibiotic use appears to be unavoidable. In these cases, ongoing clinical studies are testing ways of reverting antibiotic-induced dysbiosis: fecal microbiota transplantation (NCT03353402, NCT03341143, NCT04116775, NCT04163289), microbial ecosystem therapeutics (NCT03686202) and probiotics (NCT03637803, NCT03829111), for example.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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Authors’ contributions

PYC, NB, NP, and EC conceived and designed the study. PYC and EC analyzed the data. PYC, NB, MCLD, NP, and EC interpreted the results. PYC, NB, and EC drafted the manuscript. All authors critically reviewed or revised the manuscript.

All the authors read and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Availability of data and material

Requests for access to the data can be submitted to the corresponding author.

Abbreviations

CI	Confidence interval
C1	First ever course of ipilimumab
CCAM	French common classification of medical procedures
CDU	French common dispensing unit
HR	Hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10 th revision
ICI	Immune checkpoint inhibitor
INCA	French National Cancer Institute
IQR	Interquartile range
PMSI	French National Hospital Discharge Summary Database
SD	Standard deviation

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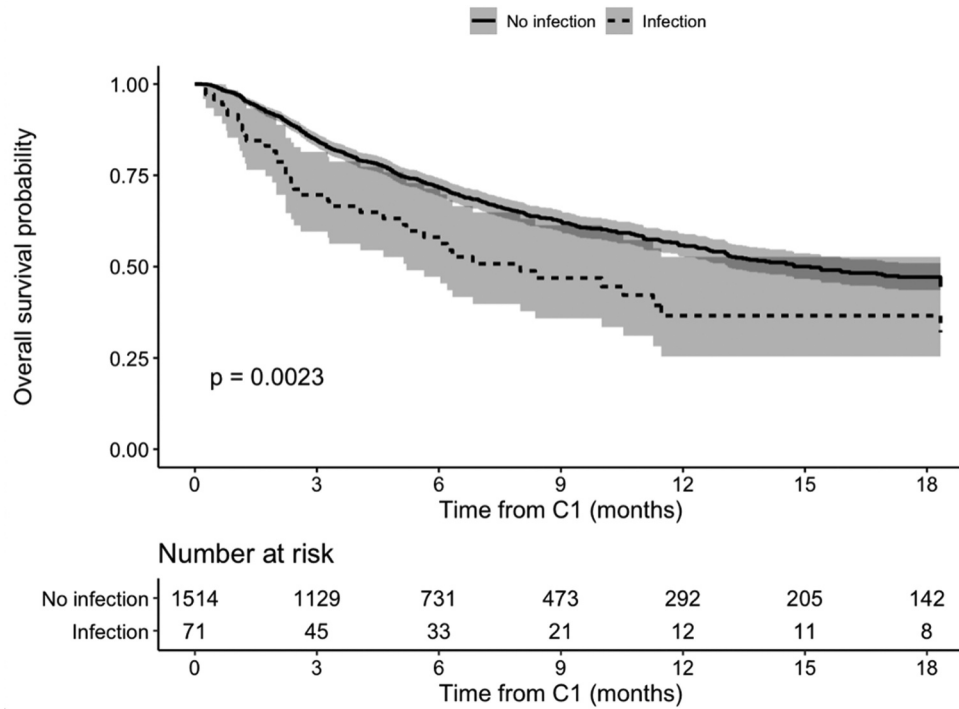
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Appendix 1. ICD-10 codes for the diagnosis of bacterial infections considered to be very strongly associated with the administration of antibiotics

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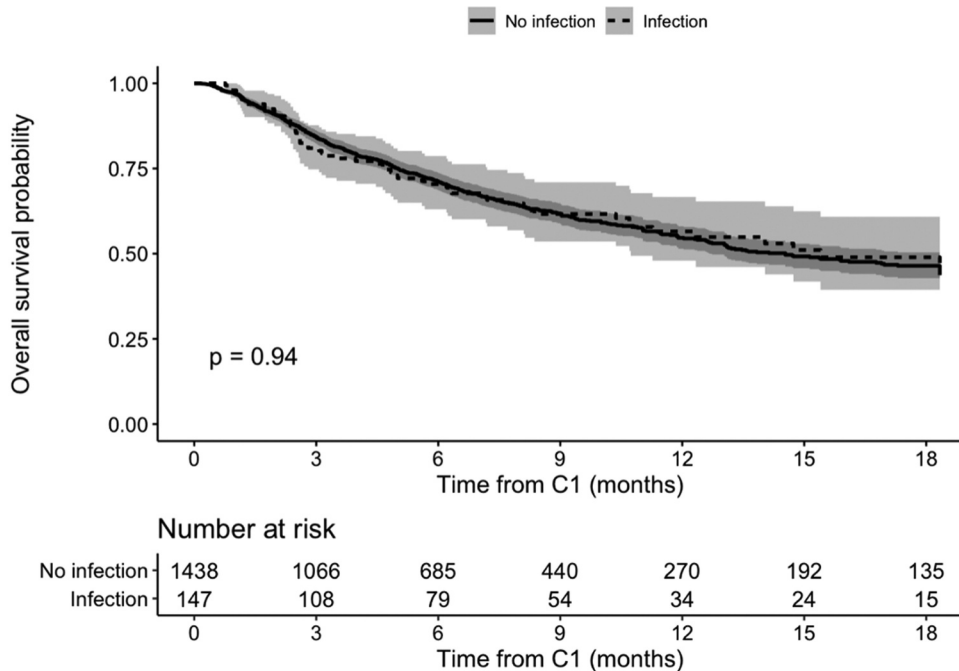
L048 L049 L050 L080 L88 M00 M000 M0000 M0001 M0002 M0003 M0004 M0005 M0006 M0007 M0008 M0009 M001 M0010 M0011 M0012 M0013 M0014 M0015 M0016 M0017 M0018 M0019 M002 M0020 M0021 M0022 M0023 M0024 M0025 M0026 M0027 M0028 M0029 M008 M0080 M0081 M0082 M0083 M0084 M0085 M0086 M0087 M0088 M0089 M009 M0090 M0091 M0092 M0093 M0094 M0095 M0096 M0097 M0098 M0099 M01 M010 M0100 M0101 M0102 M0103 M0104 M0105 M0106 M0107 M0108 M0109 M011 M0110 M0111 M0112 M0113 M0114 M0115 M0116 M0117 M0118 M0119 M012 M0120 M0121 M0122 M0123 M0124 M0125 M0126 M0127 M0128 M0129 M013 M0130 M0131 M0132 M0133 M0134 M0135 M0136 M0137 M0138 M0139 M13 M462 M4620 M4621 M4622 M4623 M4624 M4625 M4626 M4627 M4628 M4629 M463 M4630 M4632 M4633 M4634 M4635 M4636 M4637 M4638 M4639 M464 M4640 M4642 M4643 M4644 M4645 M4646 M4647 M4648 M4649 M465 M4650 M4651 M4652 M4653 M4654 M4655 M4656 M4657 M4658 M4659 M492 M4920 M4921 M4922 M4923 M4924 M4925 M4926 M4927 M4928 M4929 M630 M650 M6500 M6501 M6502 M6503 M6504 M6505 M6506 M6507 M6508 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Appendix 2. Kaplan-Meier overall survival in a sensitivity analysis



Appendix 2. Kaplan-Meier overall survival in a sensitivity analysis

Appendix 3. Kaplan-Meier overall survival in a negative control analysis



Appendix 3. Kaplan-Meier overall survival in a negative control analysis