**Prevalence and in-hospital outcomes of patients with malignancies undergoing de novo cardiac electronic device implantation in the United States**

Short Title: CIED implantation outcomes in cancer patients and survivors

Mohamed O. Mohamed, MRCP(UK)1,2, Ana Barac, MD, PhD3, Tahmeed Contractor, MD4, Helme Silvet, MD5, Ruben Casado Arroyo, MD, MSc, PhD6, Purvi Parwani, MD4, Chun Shing Kwok, MRCP(UK)1,2, Glen P. Martin, PhD7, Ashish Patwala, MD2, Mamas A. Mamas, DPhil1,2,8

1. Keele Cardiovascular Research Group, Centre for Prognosis Research, Institutes of Applied Clinical Science and Primary Care and Health Sciences, Keele University, UK
2. Royal Stoke University Hospital, Stoke-on-Trent, UK
3. Department of Cardio-Oncology, MedStar Heart and Vascular Institute, Washington, USA
4. Division of Cardiology, Department of Medicine, Loma Linda University Health, Loma Linda, CA, USA
5. Department of Cardiology, VA Loma Linda Healthcare System, CA, USA
6. Department of Cardiology, CUB Hopital Erasme, Université Libre de Bruxelles, Belgium
7. Division of Informatics, Imaging and Data Science, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
8. Institute of Population Sciences, University of Manchester, United Kingdom

Correspondence to:

Mamas A. Mamas

Professor of Cardiology

Keele Cardiovascular Research Group,

Centre for Prognosis Research,

Institute for Primary Care and Health Sciences,

Keele University, UK

mamasmamas1@yahoo.co.uk

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# Abbreviations

CIED Cardiac implantable electronic device(s)

CRT Cardiac resynchronization therapy

ICD Implantable cardioverter defibrillator

MACE Major Adverse Cardiovascular Events

PPM Permanent pacemaker

OR Odds Ratio

# Abstract

**Aims:** To study the outcomes ofcancer patients undergoing cardiac implantable electronic device (CIED) implantation.

**Methods:** De novo CIED implantations (2004 to 2015; n=2,670,590) from the National Inpatient Sample were analysed for characteristics and in-hospital outcomes, stratified by presence of cancer (no cancer, historical and current cancers) and further by current cancer type (haematological, lung, breast, colon and prostate).

**Results:** Current and historical cancer prevalence has increased from 3.3% to 7.8%, and 5.8% to 7.8%, respectively between 2004 to 2015. Current cancer was associated with increased adjusted odd ratios (OR) of MACE (composite of all-cause mortality, thoracic and cardiac complications, and device-related infection; OR 1.26, 95% confidence interval (CI) 1.23,1.30), all-cause mortality (OR 1.43, 95%CI 1.35,1.50), major bleeding (OR 1.38, 95%CI 1.32,1.44) and thoracic complications (OR 1.39, 95%CI 1.35,1.43). Differences in outcomes were observed according to cancer type, with significantly worse MACE, mortality and thoracic complications with lung and haematological malignancies, and increased major bleeding in colon and prostate malignancies. The risk of complications was also different according to CIED subtype.

**Conclusion:** The prevalence of cancer patients amongst those undergoing CIED implantation has significantly increased over 12 years. Overall, current cancers are associated with increased mortality and worse outcomes, especially in patients with lung, haematological and colon malignancies whereas there was no evidence that historical cancer had a negative impact on outcomes.

**Key Words:** Cardiac devices, pacemakers, defibrillator, cardiac resynchronization, cancer, malignancy, outcomes

**Condensed Abstract (<50 words)**

In this study we examined CIED procedural outcomes over 12 years and show that the prevalence of cancer patients has significantly increased amongst those undergoing CIED implantation. Overall, current cancers are associated with increased mortality and worse outcomes, especially in patients with lung, haematological and colon malignancies.

**What’s new?**

* The first study to examine prevalence and outcomes of de novo CIED implantations in cancer patients.
* The prevalence of current cancer patients has significantly increased amongst those undergoing implantation of all device types (PPM, CRT and ICD).
* Current cancers are associated with significantly worse mortality and in-hospital complications compared to no or historical cancer patients.
* Risk stratification according to type of device implanted and cancer site ais important to reliably prognosticate outcomes, as are strategies to address the inherent risk of complications in this population.

**Introduction**

The incidence of cancer is significant, with more than 18 million new cases diagnosed worldwide in 2018. 1 It is estimated that more than 15 million people were living with cancer in the United States (US) in 2016, and cancer remains the second leading cause of death. 2 While advances in the treatment of cancers, involving chemotherapy, radiotherapy and targeted cancer therapeutics, have increased life expectancy, they are frequently associated with cardiovascular adverse effects including heart failure, myocardial ischaemia and arrhythmias. 3-5 Additionally, patients with cancer often have pre-existing cardiovascular risk factors and comorbidities which may act in synergism with cancer therapies to precipitate overt cardiovascular toxicity. Management of arrhythmias can be challenging in patients with cancer, in particular during active treatment which may pose a continued risk of potentially life-threatening cancer-treatment induced arrhythmias (CTIA) and conduction abnormalities.4 A proportion of these patients will require cardiac implantable electronic device (CIED) therapy for the management (or primary prevention) of serious rhythm abnormalities, including permanent pacemakers (PPM) and implantable cardioverter-defibrillators (ICD), and advanced heart failure using cardiac resynchronization therapy (CRT).6, 7 While there has been a growing interest in the study of outcomes of cancer patients undergoing certain cardiovascular procedures who were shown to be at a higher risk of adverse events including mortality, bleeding and stroke, 8, 9 there is a lack of outcomes data in this population undergoing CIED implantation.

The present study sought to examine the prevalence of patients with a historical or current diagnosis of primary malignancy amongst those undergoing de novo CIED implantation procedures, and their procedural outcomes, in a US nationwide sample of hospitalizations between 2004 and 2015.

**Methods**

*Data Source*

The National Inpatient Sample (NIS) is the largest publicly available all-payer database of hospitalized patients in the United States and is sponsored by the Agency for Healthcare Research and Quality as a part of the Healthcare Cost and Utilization Project (HCUP).10 It includes anonymized data on primary and secondary discharge diagnoses and procedures from more than 7 million hospitalizations annually. The NIS dataset was designed to approximate 20% stratified sample of United States hospitals and provides sampling weights to calculate national estimates that represent more than 95% of the US population. The estimates of hospital characteristics, numbers of discharges, length of stay, and in-hospital mortality from the HCUP Nationwide Inpatient Sample (NIS) were highly comparable to three related data sources in a previous analysis: the American Hospital Association (AHA) Annual Survey Database, the National Hospital Discharge Survey (NHDS) from the National Center for Health Statistics, and the MedPAR inpatient data from the Centers for Medicare and Medicaid Services (CMS). 11

*Study Design and Population*

All de novo CIED implantation cases during hospitalizations from January 2004 through September 2015 were retrospectively analysed. CIED procedure type (PPM, CRT, and ICD), patient characteristics, comorbidities, and clinical outcomes were extracted from NIS using the International Classification of Diseases, ninth revision (ICD-9) procedure and diagnosis codes provided in the supplements (Table S1). Historical and current cancer diagnoses were extracted using ICD-9 and Clinical Classification Software (CCS) diagnoses codes, respectively (Table S2). Historical cancer cases were defined as those without an active malignancy. Missing records (n=19,155, 3% of dataset) for age, gender, admission or discharge date, length of stay and mortality were excluded from the analysis, as were any cases of device upgrades or generator replacements and any hospitalizations where other procedures had taken place (e.g. coronary angiography, percutaneous coronary intervention and coronary artery bypass grafting). A flow diagram illustrating the selection process and missing variable in the present study is presented in the supplements (Figure S1).

Procedural data and clinical outcomes other than in-hospital all-cause mortality were extracted using the relevant ICD-9 and CCS diagnosis and procedure codes (see supplements - Table S1); major bleeding, cardiac and thoracic complications, and device-related infection.

*Outcomes*

The main objective was to examine in-hospital rates of all-cause mortality and procedural-related complications (major bleeding, thoracic and cardiac complications, and device-related infection) between 1) historical and current cancer groups and 2) most prevalent cancer types (prostate, lung, colon, breast and haematological) compared to patients without cancer. All analyses were stratified by type of CIED that was implanted. Haematological malignancies included lymphomas (Hodgkin’s and non-Hodgkin’s), leukaemias and multiple myeloma. Major bleeding was defined as any intracranial, gastrointestinal or post-procedural haemorrhage according to ICD-9 diagnosis codes specified in the supplements (Table S1). Thoracic complications were defined as a composite of acute pneumothorax or haemothorax, with or without drainage, or thoracic vascular injury whereas cardiac complications were defined as a composite of cardiac tamponade, hemopericardium and pericardiocentesis.

*Statistical Analysis*

Statistical analysis was performed using SPSS version 26 (IBM Corp, Armonk, NY). Continuous variables are presented as medians with interquartile range (IQR) and were compared using the Kruskal-Wallis test. Categorical variables are presented as percentages and were analysed using the chi squared (X2) test. Multivariable logistic regression models were fitted using maximum likelihood estimation to examine the association of cancer timing groups (historical and current) with in-hospital outcomes, where we took the no cancer as the reference. Similarly, multivariable logistic regression was used to explore the association between the most prevalent current cancer types with each in-hospital outcome, using the no-cancer as the reference group. All associations were expressed as odds ratios (OR), with corresponding 95% confidence intervals, adjusted for the covariates mentioned in the supplements (Appendix A). Trend analyses was performed by assessing the interaction term between each cancer type and year in our logistic regression models.

**Results**

A total of 2,670,590 hospitalization records for CIED implantation were included in the analysis, including 187,387 (7.0%) patients with historical cancer and 122,620 (4.6%) patients with a current cancer. Overall, the prevalence of both historical and current cancers amongst those undergoing CIED implantation has significantly increased from 2004 to 2015, especially the current cancers that have more than doubled over this period of time (current: 3.3% to 7.8%; historical: 5.8% to 7.8%, Figure 1A). This trend was consistent across all device subgroups (PPM, CRT and ICD), except historical cancer in the ICD group which did not significantly change. (Figures 1B-1D, ptrend <0.001 for all except ICD: p=0.07). Patients with a historical or current cancer diagnosis were more likely to receive a PPM (vs. CRT or ICD) compared to those without cancer (62% of devices were PPM in no cancer group as compared to 75% in the current and 73.6% in the historical cancer group). (Table 1).

*Prevalence*

The prevalence of the most common current and historical cancer diagnoses are illustrated in Figure S2 and further listed in supplementary Table S3. Overall, the most prevalent current cancers included non-epithelial and skin (19.3%), prostate (19.1%), haematological (Hodgkin’s and non-Hodgkin’s lymphoma, leukaemia and multiple myeloma, total: 17.1%), breast (10.3%), bronchus and lung (8.0%), and colon (4.2%) malignancies. The most prevalent historical diagnoses included prostate (29.5%), breast (25.9%), colon (15.1%), bladder (6.7%), and bronchus and lung malignancies (6.0).

*Patient characteristics*

 Several key differences in patient characteristics were observed between patients with historical or current cancers and those without cancer. (Table 1) The cancer groups were predominantly older, white, with a higher median household income and less likely to be admitted electively. The prevalence of males was higher in the current cancer group and lower in the historical cancer groups compared to those without cancer. Both historical and current cancer groups had a lower prevalence of heart failure and higher prevalence of atrial fibrillation (AF), hypertension and dyslipidaemia. The current cancer group was the highest in risk, compared to both historical and no cancer groups, with respect to presence of comorbidities including renal failure, anaemia, thrombocytopaenia, coagulopathies, chronic pulmonary disease, and fluid and electrolyte disturbances. A similar pattern was observed within the individual CIED groups. (Tables S4-6) Patients with current cancer had a higher prevalence of AF, thrombocytopaenia, anaemia, coagulopathy, and renal failure compared to those without cancer. Active malignancy patients also had a lower prevalence of heart failure with the exception of the haematological malignancy group. (Table S7).

 Patients with current cancer had longer admissions compared to those with no or historical cancer (Table 1; median 5 days vs. 3 days for historical and no cancer groups). Within the current cancer groups, the longest admissions were observed in patients with lung and colon cancers (6 days each) followed by haematological malignancies (5 days) and breast and prostate cancers (4 days each). (Table S7)

*In-hospital outcomes*

 Crude adverse event rates in both cancer groups (current vs historical) are presented in Table 2, stratified by CIED subtype. In comparison to those without cancer, patients with a current diagnosis of cancer experienced significantly higher rates of mortality and post-procedure complications, including major bleeding, thoracic and cardiac complications, and device-related infection, whereas those with a historical cancer diagnosis had lower or comparable rates of such events (Table 2, p<0.001 for all). This pattern was consistent in both the total cohort (Figure 2A) and in individual CIED subtypes (Figure 2B).

 In multivariable analysis, historical cancers were not associated with an increased risk of mortality and complications (MACE, major bleeding and thoracic complications), both in the total cohort and individual CIED subgroups, compared to those without cancer, whereas current cancer groups were associated with significantly increased odds of adverse events. (Table 3, Figure 3) Two exceptions were thoracic complications in CRT patients where historical as well as current cancer diagnoses were associated with increased odds of a complication (1.16 95% CI 1.07, 1.26 and 1.34 95% CI 1.23, 1.46, p<0.001 for both), and the mortality in ICD patients with current cancer that did not differ from that in patients without cancer (OR 1.01 95% CI 0.83, 1.22, p=0.922).

*3.2 Most prevalent current cancer types*

The most prevalent current cancer types included in our analysis were haematological, breast, lung, colon and prostate malignancies. Although the crude rates of MACE, mortality and post-procedural complications in the total CIED cohort were generally higher in current cancer patients, compared to those without cancer, differences in complication rates were observed between cancer types. Patients with lung cancer experienced the highest rates of MACE (15.7%), all-cause mortality (3.6%) and thoracic complications (12.4%) whereas patients with colon cancer experienced the highest rates of major bleeding (4.0%) and patients with breast cancer had the highest rates of cardiac complications (0.3%). (Table 4, Figure 4) A similar pattern of outcomes was observed within individual CIED subgroups. (Table 4) The only exception was the CRT group where all-cause mortality and cardiac complications were highest in patients with colon and lung cancers, respectively.

After adjustment for potential confounders, differences in procedural outcomes persisted between current cancer types. (Table 5, Figure 5) Overall, patients with lung cancer experienced the worst outcomes, with 3-fold increased odds of MACE (OR 3.05 95% CI 2.87, 3.24), mortality (OR 3.20 95% CI 2.83, 3.62) and thoracic complications (OR 3.77 95% CI 3.52, 4.03) and increased odds of major bleeding (OR 1.29 95% CI 1.12, 1.49), followed by haematological malignancies, which was associated with increased odds of all complications (MACE: OR 1.45 95% CI 1.38, 1.53, mortality: OR 1.67 95% CI 1.51, 1.86, major bleeding: OR 1.22 95% CI 1.10, 1.35, thoracic complications: OR 1.61 95% CI 1.51, 1.71, p<0.001 for all). (Table 5, Figure 5) Although patients with colon and prostate cancer were at a higher risk of major bleeding, there was no evidence of higher risk of other outcomes. (Table 5) Similar patterns were observed in the PPM subgroup. In the CRT subgroup, only haematological, lung and breast malignancies were at increased odds of MACE and thoracic complications, haematological and colon malignancies associated with increased odds of mortality, and only colon cancer was associated with increased odds of major bleeding. In the ICD subgroup, only patients with haematological, lung and prostate malignancies were associated with increased odds of MACE and thoracic complications whereas mortality was only increased in patients with lung and prostate malignancy, and only colon cancer was associated with increased odds of bleeding. There were no significant differences in other outcomes between patients with the most prevalent cancer types and those without cancer in the CRT and ICD subgroups.

**Discussion**

 Our analysis of over two million de novo CIED implantations in a national cohort of US hospitalisations over a 12-year period highlights several important findings in patients with malignancies. First, we show that patients with both current and historical cancers are increasingly encountered amongst those undergoing CIED implantation with one in six procedures in 2015 undertaken in cancer patients, with this patient group more likely to receive a PPM than CRT and ICD devices. Second, we show that patients with a current cancer diagnosis are at a higher risk of adverse outcomes after CIED implantation compared to those without cancer whereas those with historical cancer were at no increased risk of adverse events other than thoracic complications in the CRT subgroup. The latter could be explained the higher number of leads implanted in CRT patients (vs. ICD and PPM), many of whom may have had chemotherapy ports and radiation in past, making vasculature more prone for injury. Finally, we highlight the differences in CIED implantation outcomes in different types of malignancies, with lung and haematological malignancies associated with a significantly increased risk of MACE, mortality, major bleeding and thoracic complications, and colon and prostate malignancies associated with increased risk of major bleeding but no increased risk of other outcomes. Our subgroup analyses also demonstrate that these differences in complications are even more pronounced within CIED subtypes.

 Advances in cancer therapies have led to a rise in the number of patients living with historical or current cancer. 12 Cancer patients are often elderly and have a high comorbidity burden,13 both of which are factors associated with worse procedural outcomes after CIED implantation.14 However, the specific impact of cancer on CIED post-procedural outcomes remains unknown, since this high-risk group is frequently excluded from clinical trials and even observational studies.15 As such, the study of CIED-related outcomes in this increasingly prevalent population is important in providing guidance to care providers of this complex group of patients and improve granularity in their discussion with patients around outcomes for informed consent and aid in decision making processes around optimal device choice and risk stratification.

 We find that patients with historical or current cancers are increasingly undergoing CIED implantation, with one in six procedures undertaken in patients with a current or a historical cancer diagnosis in 2015. This is in keeping with the overall rise in prevalence of active cancer patients and cancer survivors in the background population. 1, 2, 12 We observe that the most prevalent cancers amongst those undergoing CIED implantation are not different to those in the background population according to data from the United States and World Health Organisation (WHO), namely breast, bronchus and lung, colon, prostate and haematological malignancies, and non-melanoma skin cancers.1, 2 There are several mechanisms by which patients with these prevalent cancer types could develop conduction anomalies, including receipt of cancer specific therapies associated with cardiac dysfunction (such as conventional chemotherapy with anthracyclines, HER2 targeted agents as well as radiotherapy), direct metastases to the myocardium and conduction system, as well as other factors that are more common in patients with cancer such as fluid and electrolyte abnormalities and vagal reflex from emesis.4, 16

 Our analysis demonstrates differences in outcomes between patients with and without current cancer, with significantly worse outcomes including MACE, mortality, major bleeding and thoracic complications after CIED implantation in those with current cancer, both in the total cohort and across all CIED subgroups, whereas there was no evidence of increased risk in those with a historical cancer diagnosis. These findings persisted after adjustment for potential confounders, which demonstrates that a current cancer diagnosis or cancer-related therapies are independently associated with adverse outcomes in patients undergoing CIED implantation. Moreover, in our subgroup analysis of most prevalent cancer types we observe further differences in outcomes according to cancer subtype where patients with lung and haematological malignancies were at the highest risk of MACE and mortality while colon and prostate cancers groups experienced the highest rates of major bleeding without an increase in MACE and mortality rates. These differences in outcomes between current cancers groups are even more pronounced in CIED subgroups, including PPM, ICD and CRT, each of which have different indications, procedural complexity and risks.

In the absence of any previous published outcomes data for this population, we are unable to compare our findings to other studies. However, there are several possible reasons for the higher mortality and complication rates in patients with current cancer. First, the observed increased mortality and major bleeding could be directly related to their oncological condition. Patients with cancer are at a high risk of bleeding due to tumour angiogenesis, local tumour invasion, increased use of anticoagulation, as well as cancer-associated coagulopathies due to liver metastases, bone marrow suppression resulting in thrombocytopaenia, and cancer treatments.17 18 Second, patients with specific malignancies such as breast and lung cancers may require implantation of a CIED in a less commonly used site (other than left upper pre-pectoral region) or the use of different sites of venous access (e.g. internal jugular or subclavian more than cephalic), which could lead to increased thoracic complication rates in these patients. For example, patients with breast cancer may have undergone (or are due to undergo) modified radical mastectomy with pre-pectoral breast implants which drives operators to implant devices in the sub-pectoral region to allow creation of a pocket. Further, if there is significant lymph node dissection, laterality changes to the less favoured side. Similarly, chest radiation is a standard treatment for stages I-III invasive breast cancer and may affect tissue healing and risk of pocket infection after CIED implantation. Third, the increased risk of thoracic complications in patients with lung and breast malignancies could also be attributed to direct tumour invasion whereas increased bleeding and thoracic complications in those with haematological malignancies could be possibly explained by the increased risk of vasculitis, bleeding diathesis, drug-induced vascular effects associated with type of malignancy, cachexia associated with cancer, and radiotherapy.19

The present study has several clinical implications as it informs operators of procedural outcomes after CIED in this special population and emphasises the need for risk reduction strategies to address their inherent risk of complications. While the need for CIED therapy in patients with cancer may be unavoidable, certain strategies may help mitigate their risk of procedural complications, including ultrasound-guided venous access, cephalic cut down, echocardiographic septal-pacing confirmation and even His bundle in lieu of coronary sinus or traditional right ventricular apical pacing. Leadless pacemakers could be more widely adopted in patients who would otherwise require a PPM. Furthermore, the higher risk of infections observed in current cancer patients, especially those undergoing CRT and ICD implants, could potentially be minimised by the routine use of antimicrobial envelopes in these patients, which have been shown to reduce the overall risk of CIED-related infection. 20

*Strengths and Limitations*

This is the first study to report the prevalence of cancer patients amongst inpatients undergoing de novo CIED implantation, and provides important insights into their outcomes, stratified by timing of cancer diagnosis (historical vs. current), type of current cancer, and CIED subtype in a nationwide cohort. However, there are several limitations to the current study. First, the administrative nature of the NIS database is susceptible to coding errors, although the use of ICD-9 codes for cardiovascular outcomes research has been previously validated, including studies that examined CIED related complications. 21 Second, the NIS dataset does not provide information on laboratory values pharmacotherapy, including chemotherapy medications, which may have an impact on outcomes. NIS data also does not include the indication for the CIED (e.g. type of arrhythmia and primary vs. secondary prevention in CRT-D and ICD procedures), type of device (e.g. VVI or DDD), operator experience or procedure time. Therefore, we were unable to adjust for differences in these confounders between the study groups. Third, the NIS only reports in-hospital outcomes, so the present findings may not be applicable to longer term outcomes. While the majority of CIED-related complications arise in the peri-procedural phase, further complications can arise in cancer patients such as device malfunctioning in those requiring ongoing radiotherapy, as well as venous stenosis or thrombosis. 22 23 24 Fourth, although the present study informs us of procedural outcomes in patients with cancer from a national perspective, they may not necessarily be generalisable to the entire cancer population since there may be an element of selection bias where patients with a very poor prognosis may not be offered a CIED or are only offered a PPM. Nevertheless, we believe that this reflects real-world practice. Finally, as with most observational studies, there is an inherent risk of residual confoundments and, therefore, associations described do not necessarily infer causality.

# Conclusion

 In a nationwide analysis of de novo CIED implantation procedures, we demonstrate a rise in the prevalence of those with historical and current cancers undergoing this procedure over a 12-year period, especially the latter group who were older and more comorbid compared to those without cancer. Patients with a current cancer diagnosis, especially lung, haematological and colon malignancies, are at an increased risk of mortality and major complications after CIED implantation, while there was no evidence of worse outcomes in those with historical cancer. The utilization of CIED’s for managing conduction abnormalities that may be incident or resulting from, or precipitated by, malignancies or their therapies may be unavoidable. However, risk stratification according to the type of cancer as well as type of device is important to reliably prognosticate outcomes and employ risk reduction strategies in this high-risk population.

# Conflicts

No authors have reported any disclosures or relationships with the industry.

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# Statement

The manuscript has neither been published nor is currently under consideration for publication by any other journal. All authors have approved the final version of the manuscript.

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# Figure titles and legends

# Figure 1. Prevalence of cancer over the study period in A) total cohort and B) individual CIED subgroups

**Caption:** \*2015 only includes admissions from 1st January through 30th September; ptrend <0.001 for all except ICD: p=0.07; **ICD**: implantable cardioverter-defibrillator; **CRT:** cardiac resynchronization therapy; **PPM:** permanent pacemaker

**Figure 2. In-hospital adverse events in A) overall cohort and B) individual CIED subgroups according to timing of cancer diagnosis**

**Caption:** \*MACE: Composite of mortality, thoracic complications, cardiac complications and device-related infection; \*\*Cardiac complications occurred at a frequency less than 0.05% in the historical cancer groups; **ICD**: implantable cardioverter-defibrillator; **CRT:** cardiac resynchronization therapy; **PPM:** permanent pacemaker

**Figure 3. Adjusted odds ratios (OR) of adverse events in total cohort and according to device subtype**

**MACE:** major adverse cardiovascular events (composite of mortality, thoracic and cardiac complications and device-related infection); **ICD**: automated implantable cardioverter-defibrillator; **CRT:** cardiac resynchronization therapy; **PPM:** permanent pacemaker;

**Figure 4. In-hospital adverse events according in most prevalent cancer groups**

**Figure 5. Odds ratios (OR) of in-hospital adverse events in most prevalent cancer groups\***

**Caption:** **MACE:** major adverse cardiovascular events (composite of mortality, thoracic and cardiac complications and device-related infection); \*models adjusted for age, sex, weekend admission, primary expected payer, median household income, dyslipidaemia, smoking status, cardiac previous acute myocardial infarction, previous CABG, history of ischemic heart disease (IHD), previous percutaneous coronary intervention (PCI), previous cerebrovascular accidents (CVA) including stroke or transient ischemic attacks, family history of CAD, bed size of hospital, region of hospital, location/teaching status of hospital, year of admission, history of cardiac arrest, ventricular tachycardia and ventricular fibrillation, cardiogenic shock and the Elixhauser comorbidities: acquired immune deficiency syndrome, rheumatoid arthritis/collagen vascular diseases, congestive heart failure, chronic pulmonary disease, coagulopathy, diabetes (uncomplicated), diabetes with chronic complications, hypertension, hypothyroidism, liver disease, metastasis status, other neurological disorders, obesity, peripheral vascular disorders, valvular heart disease, and weight loss.