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Prevalence, outcomes and costs according to patient frailty status for 2.9 million cardiac electronic device implantations in the United States

--Manuscript Draft--

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Abstract:	<p>Background: Little is known about the impact of frailty on length of stay (LOS), cost and in-hospital procedural outcomes of cardiac implantable electronic device (CIED) implantation procedures.</p> <p>Methods: All de novo CIED implantations recorded in the United States (2004-2014) from a national database were stratified according to the Hospital Frailty Risk Score into low-risk (LRF;<5), intermediate-risk (IRF;5-15) and high-risk (HRF;>15) frailty groups. Regression analyses were performed to assess the association between frailty and procedural outcomes.</p> <p>Results: Out of 2,902,721 implantations, LRF, IRF and HRF were 77.6%, 21.2% and 1.2%, respectively. Frailty increased from 2004 to 2014 (IRF: 14.3% to 32.5%, HRF: 0.2% to 3.3%). Complications were 2-3 fold higher in the IRF and HRF groups, while all-cause mortality was 4 to 9-fold higher in IRF (2.9%) and HRF (5.3%) groups, depending on the type of CIED ($p<0.001$ for all). Rates of complications increased over the study years and all-cause mortality declined, especially in the higher frailty risk groups (2004 vs. 2014; Mortality: IRF:3.8 vs. 2.2%, HRF:9.9 vs. 4.5%; Bleeding: IRF:3.7 vs. 9.0%, HRF:3.9 vs. 12.2%; Thoracic: IRF:4.3 vs. 6.0%, HRF:2.9 vs. 9.1%; Cardiac: IRF:0.5 vs. 0.9%, HRF:0.5 vs. 0.9%). Rising frailty was associated with increase in cost ($p<0.001$) and LOS (median 3, 8, 11 days for LRF, IRF, HRF respectively, $p<0.001$). The cost for HRF patients receiving a defibrillator was approximately quarter million US dollars per patient.</p> <p>Conclusion: Frailty is associated with worse clinical outcomes, higher cost and LOS independent of age or CIED type. Our findings emphasize the importance of frailty assessment.</p>



Dear Professor Stanley Nattel, MD, Editor in Chief,

We thank the Editor-in-Chief and Reviewer for their valuable comments on the manuscript entitled 'Prevalence, outcomes and costs according to patient frailty status for 2.9 million cardiac electronic device implantations in the United States' and feel that these recommendations have further improved the quality of our manuscript. We have attempted to answer all the comments fully as outlined in the rebuttal and tracked all new changes in the manuscript.

Yours sincerely

Dr Mohamed Mohamed and Professor Mamas A. Mamas

On behalf of submitting authors

Editor comments:

- 1. I feel that the title could be improved. How about something more like: "Prevalence, outcomes and costs according to patient frailty status for 2.9 million cardiac electronic device implantations in the United States".**

We thank the Editor for this recommendation. The manuscript title has now been changed as per this recommendation.

Response to Reviewers

Reviewer #1:

Thank you for the opportunity to review your revised manuscript. The authors have adequately dealt with most of my comments and the body of the manuscript is satisfactory. My main comments pertain to the abstract. This should be honed in to provide the reader with all the most galvanizing aspects of the manuscript. Please see below as a suggestion if the authors agree. (and the authors can confirm the data and provide some additional numerical details to back up/flesh out the points in the abstract given the word count now is still less than the maximum).

We thank the reviewer for their suggested edit. We have adopted most of the text in our revised abstract and have added further numerical data to the abstract as per the reviewer's suggestion (below):

Background: Little is known about the impact of frailty on length of stay (LOS), cost and in-hospital procedural outcomes of cardiac implantable electronic device (CIED) implantation procedures.

Methods: All de novo CIED implantations recorded in the United States (2004-2014) from a national database were stratified according to the Hospital Frailty Risk Score into low-risk (LRF;<5), intermediate-risk (IRF;5-15) and high-risk (HRF;>15) frailty groups. Regression analyses were performed to assess the association between frailty and procedural outcomes.

Results: Out of 2,902,721 implantations, LRF, IRF and HRF were 77.6%, 21.2% and 1.2%, respectively. Frailty increased from 2004 to 2014 (IRF: 14.3% to 32.5%, HRF: 0.2% to 3.3%). Complications were 2-3 fold higher in the IRF and HRF groups, while all-cause mortality was 4 to 9-fold higher in IRF (2.9%) and HRF (5.3%) groups, depending on the type of CIED ($p<0.001$ for all). Rates of complications increased over the study years and all-cause mortality declined, especially in the higher frailty risk groups (2004 vs. 2014; Mortality: IRF:3.8 vs. 2.2%, HRF:9.9 vs. 4.5%; Bleeding: IRF:3.7 vs. 9.0%, HRF:3.9 vs. 12.2%; Thoracic: IRF:4.3 vs. 6.0%, HRF:2.9 vs. 9.1%; Cardiac: IRF:0.5 vs. 0.9%, HRF:0.5 vs. 0.9%). Rising frailty was

associated with increase in cost ($p < 0.001$) and LOS (median 3, 8, 11 days for LRF, IRF, HRF respectively, $p < 0.001$). The cost for HRF patients receiving a defibrillator was approximately quarter million US dollars per patient.

Conclusion: Frailty is associated with worse clinical outcomes, higher cost and LOS independent of age or CIED type. Our findings emphasize the importance of frailty assessment.

Reviewer #3:

The authors have responded to and revised the manuscript well. I have no further comments to make. Thank you for your excellent contribution.

We thank the reviewer for their kind comments as well as for all the valuable recommendations they have made to improve our initial submission.

Prevalence, outcomes and costs according to patient frailty status for 2.9 million cardiac electronic device implantations in the United States

Short Title: Effect of frailty on CIED implantation outcomes.

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Conflicts

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Abbreviations

CIED	Cardiac Implantable Electronic Device(s)
CRT	Cardiac resynchronization therapy
HRF	High-risk frailty
ICD	Implantable cardioverter defibrillator
IRF	Intermediate-risk frailty
LRF	Low-risk frailty
MACE	Major Adverse Cardiovascular Events
PPM	Permanent pacemaker
OR	Odds Ratio

Abstract

Background: Little is known about the impact of frailty on length of stay (LOS), cost and in-hospital procedural outcomes of cardiac implantable electronic device (CIED) implantation procedures.

Methods: All de novo CIED implantations recorded in the United States (2004-2014) from a national database were stratified according to the Hospital Frailty Risk Score into low-risk (LRF;<5), intermediate-risk (IRF;5-15) and high-risk (HRF;>15) frailty groups. Regression analyses were performed to assess the association between frailty and procedural outcomes.

Results: Out of 2,902,721 implantations, LRF, IRF and HRF were 77.6%, 21.2% and 1.2%, respectively. Frailty increased from 2004 to 2014 (IRF: 14.3% to 32.5%, HRF: 0.2% to 3.3%). Complications were 2-3 fold higher in the IRF and HRF groups, while all-cause mortality was 4 to 9-fold higher in IRF (2.9%) and HRF (5.3%) groups, depending on the type of CIED ($p<0.001$ for all). Rates of complications increased over the study years and all-cause mortality declined, especially in the higher frailty risk groups (2004 vs. 2014; Mortality: IRF:3.8 vs. 2.2%, HRF:9.9 vs. 4.5%; Bleeding: IRF:3.7 vs. 9.0%, HRF:3.9 vs. 12.2%; Thoracic: IRF:4.3 vs. 6.0%, HRF:2.9 vs. 9.1%; Cardiac: IRF:0.5 vs. 0.9%, HRF:0.5 vs. 0.9%). Rising frailty was associated with increase in cost ($p<0.001$) and LOS (median 3, 8, 11 days for LRF, IRF, HRF respectively, $p<0.001$). The cost for HRF patients receiving a defibrillator was approximately quarter million US dollars per patient.

Conclusion: Frailty is associated with worse clinical outcomes, higher cost and LOS independent of age or CIED type. Our findings emphasize the importance of frailty assessment.

Key Words: Cardiac devices, pacemakers, defibrillators, cardiac resynchronization, frailty, risk scores, trends, outcomes, treatment

Condensed Abstract

The effect of frailty on clinical outcomes of patients undergoing CIED implantations remains unknown. In this study, we show that the prevalence of frailty has increased from 2004 to 2014 and that patients with intermediate and high-risk frailty are associated with higher mortality and worse procedure-related complications after CIED implantations. Our findings emphasize

the importance of incorporating frailty assessment into routine clinical practice when assessing patients undergoing CIED implantations.

Introduction

The association between frailty and cardiovascular outcomes has become increasingly recognized in recent years. [1](#) [2](#) [3](#) Frailty is defined as “a clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with everyday or acute stressors is compromised”. [4](#) Although frailty is synonymously used with ageing and multimorbidity in clinical practice, not all frail individuals suffer from chronic conditions or advanced age.[5](#) [6](#) Several studies have demonstrated that young patients with chronic illnesses and multimorbidity are also considered ‘biologically frail’ [7](#), and up to 7% of frail individuals have no common chronic conditions, while 25% of frail individuals have only one chronic condition.[5](#)

Cardiac implantable electronic devices (CIED), including permanent pacemakers (PPM) and implantable cardioverter-defibrillators (ICD), are important in the management of serious rhythm abnormalities. CIEDs also include cardiac resynchronization therapy with pacemaker alone (CRT-P) or with defibrillator (CRT-D) that play an important role in the management of patients with advanced heart failure refractory to optimal medical therapy. [8](#)-[10](#) The prevalence and clinical outcomes of frail patients undergoing CIED implantation has not been previously studied nationally as these patients are frequently excluded from randomized trials. Consequently, little is known about the effect of frailty on clinical outcomes, and whether these outcomes differ according to the type of CIED implanted. Few studies have looked at the prevalence or associated outcomes of frailty in cardiac devices, [[3](#), [21](#), [22](#)] but these have been limited by their analyses of specific types of CIED procedures (e.g. ICD) in patients with certain indications (e.g. primary prevention) or in highly specialized centers, rendering their findings as poorly representative of the background population of CIED

implantations. In addition, the majority of studies investigating cardiovascular outcomes in frail patients had only included elderly patients^{2, 3, 11} while excluding younger and comorbid patients who may be biologically frail⁷.

While numerous frailty scores exist, no single score is considered a gold standard.¹² The majority of scores require clinical evaluation of patients, which is often challenging and time-consuming in the acute setting, and cannot be computed from administrative datasets. The Hospital Frailty Risk Score (HFRS) was recently introduced as a means to score frailty from administrative data¹³ and was validated against two prominent scores: Fried Frailty Phenotype and Rockwood Frailty Index. In the present study we utilized the HFRS to study trends in frailty in the United States over a ten-year period and examine its effect on clinical outcomes of de novo CIED implantation procedures according to the type of CIED used.

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).¹⁴ Further information on its structure and validation is available in the supplements (Appendix A)

Study Design and Population

All hospitalizations during which de novo CIED implantations were performed were retrospectively analyzed. CIED procedures (PPM, CRT-P, CRT-D, 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). Furthermore, using ICD-9 equivalents of the ICD-10

codes that make up HFRS, each patient was assigned a score and stratified into one of three risk groups; Low-Risk Frailty (LRF; <5), Intermediate-Risk Frailty (IRF; 5-15) and High-Risk Frailty (HRF; >15) (Table S2). Missing records (n=18,321, 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. 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, length of stay and total charges were extracted using the relevant ICD-9 and Clinical Classification Software (CCS) diagnosis and procedure codes (see supplements - Table S1); procedure-related bleeding, cardiac complications and thoracic complications.

Outcomes

The primary outcome measures were in-hospital rates of all-cause mortality, major acute cardiovascular events (MACE), and procedural-related complications (bleeding, thoracic and cardiac complications) between frailty risk groups according to type of CIED implanted. In-hospital MACE was defined as a composite of all-cause mortality, thoracic and cardiac complications, device-related infection and reoperation. Procedure-related bleeding was defined as any post-procedural hemorrhage according to ICD-9 diagnosis codes specified in the supplements (Table S1). Thoracic complications were defined as a composite of acute pneumothorax or hemothorax, with or without drainage, or thoracic vascular injury, while cardiac complications were defined as a composite of cardiac tamponade, hemopericardium, pericardiocentesis.

The secondary outcome was to evaluate the economic burden of CIED implantations in patients with intermediate and high risk of frailty compared to those with a low risk of frailty as measured by length of stay and total hospitalization charges, measured in US Dollars (USD).

Statistical Analysis

Statistical analysis was performed using SPSS version 24 (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 analyzed using the chi-squared (X^2) test.

Multivariable logistic regression models were fitted using maximum likelihood estimation to examine the association of frailty with each in-hospital outcome (all-cause mortality and individual complications) using low-risk frailty as the reference category in the form of odds ratios (aOR), and adjusting for all covariates that were not part of the HFRS as mentioned in the supplements (Appendix B). The model fits were assessed using the Hosmer-Lemeshow statistic, [15](#) and all models were able to correctly classify at least 97% of those who experienced the outcome being assessed.

A sensitivity analysis of clinical outcomes stratified by patient age (greater or less than 75 years) was conducted to ensure that these outcomes were not drastically different in younger patients.

Results

A total of 2,902,721 hospitalizations were recorded during which patients underwent de novo CIED implantation in the United States between 2004 and 2014. The proportion of patients in the low, intermediate and high frailty risk groups were 77.6%, 21.2% and 1.2%, respectively. Figure 1a illustrates a rise in prevalence of frailty amongst patients undergoing CIED implantation over the study decade, as evidenced by a rise in IRF and HRF groups from 2004 to 2014 (IRF: 14.3% to 32.5% and HRF: 0.2% to 3.3%). The rising trend of frailty over the study years was observed in all types of CIED (Figure 1b). The most common procedure in all study groups was PPM insertion, followed by ICD, CRT-D and finally CRT-P (Table

S3). There was a shifting trend towards more complex device implantations in HRF patients over the study period (Figure 1c).

Several differences in patient demographics are observed between the frailty risk groups of the entire CIED cohort (Table S3, $p < 0.001$ for all). Patients with IRF and HRF were generally older and less likely to be male or caucasian, and more likely to have a history of arrhythmias such as ventricular fibrillation, atrial fibrillation, and cardiac arrest. Although higher frailty risk groups (IRF and HRF) had a higher prevalence of certain cardiovascular risk factors such as complicated diabetes, previous cerebrovascular accidents (CVA), hypertension and valvular heart disease, they were less likely to have had a history AMI or have undergone previous percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The demographic differences between frailty risk groups were also similar in the subgroup analyses of individual devices (PPM, CRT-P, CRT-D and ICD; Tables S4-S6).

In-hospital adverse outcomes

The overall rates of MACE and all-cause mortality were 5% and 1%, respectively, with a frequency of procedure-related complications (thoracic and cardiac complications, and bleeding) varying between 0.4% and 3% (Table 1, Figure 2).

The unadjusted rates of all-cause mortality, thoracic and cardiac complications, and procedure-related bleeding were significantly higher in the IRF and HRF groups compared to the LRF group in the entire CIED cohort (IRF and HRF vs. LRF; all-cause mortality: 2.9% and 5.3% vs. 0.4%, thoracic: 5.2% and 7.5% vs. 2.3%, cardiac: 0.7% and 0.7% vs. 0.3%, bleeding: 6.0% and 8.7% vs. 2.0%; $p < 0.001$ for all, Table 1, Figure 2) as well as in each CIED subgroup (see supplements - Table S7, Figure 3). The rates of in-hospital MACE increased over the study years in all the frailty groups, primarily driven by a rise in the incidence of bleeding and thoracic complications, especially in the higher risk frailty groups where these complications

increased by two to three folds (IRF and HRF, Figure 4, Table S8). In contrast, all-cause mortality has decreased over the study years, particularly in the higher risk groups (IRF and HRF, Figure 4, Table S8).

Device-related infection was more than three-fold higher in IRF and HRF groups compared to the LRF group, but there was no statistically significant difference between the higher risk groups (IRF vs. HRF: 2.0% vs. 1.9%) (Table 1, Figure 2). The higher risk of device related infection in both IRF and HRF groups was consistent across all CIED subtypes compared to the LRF group, but was exceptionally higher in frail patients (IRF and HRF) undergoing complex device implantation (CRT-D, CRT-P and ICD) compared to those undergoing pacemakers (Table S7, Figure 3). The higher frailty groups were more likely to undergo pocket revision (IRF:1.5% and HRF: 1.6% vs. LRF 1.0%, $p<0.001$) but less likely to undergo lead revision (IRF:1.5% and HRF: 1.4% vs. LRF 1.6%, $p=0.003$) compared to the lower frailty group. (Table 1).

After adjustment for baseline differences, the higher risk of adverse events in the IRF and HRF groups persisted in multivariate analysis (Table 2). The overall odds of any complication (MACE) was two to three-fold higher in IRF and HRF groups compared to LRF group, regardless of the type of implanted device (Table 2, Figure 5). Patients with IRF and HRF were significantly associated with higher odds of all-cause mortality in the same admission after receiving a CIED (at least 4-fold and 7-fold respectively) compared to those with LRF, irrespective of the type of CIED. All-cause mortality was significantly higher in the HRF group than the IRF group in most device groups (PPM, CRT-P and ICD), although in patients undergoing CRT-D procedures both groups were at a seven-fold increased odds of all-cause mortality compared to the LRF group (IRF aOR: 6.83 [6.16, 7.58]; HRF aOR: 7.06 [5.41, 9.21], $p<0.001$ for both).

The adjusted odds of procedure-related bleeding and other complications (thoracic and cardiac) were significantly higher (≥ 1.5 fold) in patients with IRF and HRF when compared to the LRF group (Figure 5), with the exception of cardiac complications in patients undergoing CRT-P implantation (4-fold increased odds in IRF and HRF groups) and ICD (insignificant odds in HRF patients: aOR 1.12 [0.98,1.21], $p=0.07$).

Frailty was the strongest independent predictor of adverse events in patients undergoing CIED implantation, with other independent predictors presented in supplements (Table S9).

Total hospitalization charges and length of stay

The median total hospitalization charges for the entire cohort were USD 71,641 (USD 42,142, USD 120,910), ranging from USD 51,109 (USD 34,352, USD 82,306) for PPM procedures to USD 124,613 (USD 91,733, USD 174,779) in CRT-D procedures (see supplements - Table S7). Median hospitalization charges were approximately 1.5 and 2-folds higher in IRF and HRF groups, respectively, compared to the LRF group, in all CIED subtypes (Table S7).

The mean length of stay for any CIED implantation procedures was prolonged significantly as the frailty risk increased, with IRF and HRF patients experiencing 2-3 folds longer admissions, regardless of the type of CIED implanted, compared to LRF patients (Table S7).

Sensitivity Analysis

A sensitivity analysis of clinical outcomes stratified by patient age (less or greater than 75 years) was performed (Table S10). The proportion of patients younger than 75 years at the time of CIED implantation was 48% ($n=1,351,900$). At least one in six young patients (<75 years; 17.4%) was classified as intermediate-risk frailty, and 0.8% of young patients were high-risk frailty.

All adverse events were higher in IRF and HRF groups in both young and old patients (Table S6) in line with the findings observed in the entire cohort.

Discussion

The present study, drawn from a contemporary cohort of almost 3 million hospitalizations in the United States, is the first to report national estimates of the prevalence and in-hospital clinical outcomes of de novo CIED implantations according to frailty risk groups. We found a rise in the prevalence of frailty amongst patients undergoing CIED with a rise in intermediate-risk and high-risk frailty patients from 14.3% to 32.5% and 0.2% to 3.3%, respectively between 2004 and 2014. Patients with intermediate and high-risk frailty compared to those with low-risk frailty, regardless of the type of CIED implanted and patient age, had significantly worse in-hospital outcomes after CIED implantation procedures, including all-cause mortality, infection, procedure-related bleeding, and thoracic and cardiac complications. Finally, we highlight the economic burden of frailty on healthcare facilities where patients undergo CIED implantation procedures where the length of stay and hospitalization charges of patients with intermediate-risk and high-risk frailty were notably higher than in patients with low-risk frailty.

The present study is the first to examine the prevalence of frailty in an unselected and contemporary national cohort of CIED implantations over a decade and shows a significant rise in the prevalence of intermediate and high risk frailty patients receiving such procedures over the study period. A European Heart Rhythm Association (EHRA) survey recently showed that less than 10% of patients undergoing CIED implantations in European centers are considered prefrail or frail. [11](#) However, the definition of frailty and the study findings were based on physicians' own opinions without the use of a standardized assessment tool for frailty. Another study by Kramer et al. reported a frailty prevalence of 12.8% amongst patients with

CIED's implanted more than 2 months before prior to attending an ambulatory device clinic in a tertiary center in the United States, although their inclusion cohort (n=219) represented less than half of patients who attended their ambulatory device clinic (n=448).[16](#)

Our findings suggest worse clinical outcomes and higher all-cause mortality in frail patients undergoing CIED implantations, regardless of the type of CIED they receive, and of their age. In-hospital mortality all-cause in patients with intermediate and high-risk frailty was five to nine-fold higher than in low-risk frailty patients, depending on the type of CIED implanted, while other complications were between 50% and 150% more likely to occur in intermediate and high risk frailty patients in the total CIED cohort. Furthermore, we observe a rise in the incidence of procedure-related complications and a decline in all-cause mortality over the study years, especially in patients with higher-risk frailty. The observed upward trend in complications is in line with more complex device implantations, while the decline in mortality is likely due to advancements in specialized geriatric care provided to more frail patients or better case selection.[17](#) A study of Medicare patients with heart failure undergoing primary prevention ICD implantation between 2006 and 2009 reported significantly higher one-year mortality in frail patients compared to those without any medical conditions other than heart failure (22% vs. 4%).[3](#) Although their analysis provided insight in to the outcomes of this specific population, it was derived from decade-old data and was not representative of contemporary older age ICD populations. Similarly, an analysis of CIED implantations between 1997 and 2004 in the United States reported higher in-hospital mortality and all-cause complications in patients who were classified as frail according to the authors' own definitions, indicated by advanced age, comorbidity burden and emergency admission. [18](#) Our analysis suggests that frailty is associated with adverse outcomes irrespective of the CIED device implanted, with similar risk of adverse outcomes associated with both defibrillator (ICD and CRT-D) and non-defibrillator (PPM and CRT-P) devices in frail patients. These findings could

be relevant to cardiologists when deciding on the type of device in frail patients who may otherwise be eligible for a defibrillator therapy, and whom are currently much less likely to receive a defibrillator device according to a recent EHRA survey.[11](#) An interesting finding in our subgroup analysis is the higher rate of in-hospital all-cause mortality in patients undergoing PPM and CRT-P implantations, which probably demonstrates cardiologists' selection of patients who are more likely to benefit from more complex device implantation.

There was a significant disparity in rates of device-related infection between frailty groups as well as between different CIED subtypes. Higher frailty groups were more likely to experience such a complication compared to the low frailty group, an observation that was consistent across all CIED subtypes. Noteworthy, there rates of device-related infection were significantly higher in intermediate and high-risk frail patients undergoing complex device therapy (CRT-P, CRT-D and ICD; 2.6-5.3%) compared to those undergoing pacemaker implantation (1.4%). While the knowledge of procedure-specific information is vital in explaining the observed differences, there are several justifications for the higher rates of infection in complex device groups, especially in higher risk frailty patients. Complex device implantation is often associated with longer procedural time and more prolonged lead manipulation, which is known to predispose to more venous damage, secondary inflammation and, in turn, infection.[19](#) [20](#) More frail patients are more susceptible to such processes due to their reduced host defense and resistance to infections.[21](#) [22](#) Our present findings emphasize the importance of frailty assessment from an economic perspective since device-related infections are associated with significant cost implications.[23](#) We believe that our study informs clinicians of more accurate rates of overall complications and the need for repeat procedures depending on the patient's frailty score. For example, patients with a higher risk of frailty may be more likely to require pocket revision as demonstrated in our analysis, which is

more likely in these patients due to their increased tissue fragility and thinner layer of subcutaneous fat.[24](#)

Our study is the first to highlight the economic burden of CIED implantations in frail patients. We show that total hospitalization charges of CIED implantation admissions were significantly higher (50-100%) in patients with intermediate and high-risk frailty, with an incremental rise in costs as the risk of frailty increases. Hospitalizations where high-risk frailty patients received CRT-D and ICD devices cost almost a quarter million US dollars per patient. This could be possibly attributed to the higher rate of complications in higher risk (intermediate and high risk) groups that often require prolonged and more intensive management as evidenced by a longer length of stay (two to three folds longer in intermediate and high-risk frailty compared to low risk frailty patients). These findings raise questions about the sustainability of offering such devices to frail patients, most of which receiving public insurance (Medicare and Medicaid), and whether these therapies have an impact on their life quality and expectancy in view of their high rates of all-cause mortality. While pre-habilitation in patients with frailty has been shown to improve outcomes in patients undergoing some procedures[25](#), it is unclear whether targeting frailty in patients that are due to undergo CIED implantation electively may contribute to better outcomes. Future studies should consider this across a spectrum of cardiovascular disorders.

Limitations

There are several limitations to our study. First, the administrative nature of the NIS database, as with any such database has limitations around the accuracy of coding with no external validation. However, the use of ICD-9 codes from such databases has been previously validated for the purpose of cardiovascular research [26](#) Second, since the NIS dataset does not provide information on pharmacotherapy, indication for each CIED device (e.g. type of arrhythmia and primary vs. secondary prevention in CRT-D and ICD procedures), type of

pacemaker (dual chamber versus biventricular pacemaker), operator experience and procedure time, we were unable to adjust for the differences in these covariates between the study groups. Third, the HFERS was validated in patients over the age of 75, however, our sensitivity analysis demonstrated similar outcomes between younger (<75 years) and older (>75 years) patients. Fourth, since the majority of elective CIED implantations are performed in the outpatient setting, which is not captured in NIS. It is likely that the distribution of frailty and subsequent outcomes are different in patients admitted electively but we are unable to demonstrate this contrast from the present dataset. Finally, the NIS only reports in-hospital outcomes and so the present findings may not be applicable to longer term outcomes although the majority of complications have been shown to occur in the peri-procedural and early post procedural phase.

Conclusion

The present nationwide analysis of CIED implantations in the United States shows that intermediate-risk and high-risk frailty, as defined by the Hospital Frailty Risk Score, has increased significantly over the study decade and has become more common amongst patients undergoing these procedures. Frailty is associated with significantly worse post-procedural outcomes and higher all-cause mortality in patients undergoing CIED implantation regardless of their age. Our findings support the incorporation of an objective frailty risk score into the routine risk assessment of patients undergoing such procedures to support shared decision-making and improve prognostication around their procedural risk and anticipated outcomes.

Conflicts

DB is paid by Medtronic for educational sessions. Other co-authors have no disclosures and no relationships with the pharmaceutical 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 1a. Prevalence of frailty amongst patients undergoing CIED implantations (2004-2014)

Legend:

HRF: High-risk frailty; IRF: Intermediate-risk frailty; LRF: Low-risk frailty

Figure 1b. Prevalence of frailty according to type of CIED

Legend:

HRF: High-risk frailty; IRF: Intermediate-risk frailty; LRF: Low-risk frailty

Figure 2. In-hospital adverse events of frailty groups in total cohort

Legend:

*Comp: complications; $p < 0.001$ for all outcomes; **MACE**: Composite of mortality, thoracic and cardiac complications, device-related infection and reoperation.

Figure 3. In-hospital adverse events in frailty groups according to type of CIED

Legend:

*Comp: complications; $p < 0.001$ for all outcomes; **ICD**: automated implantable cardioverter-defibrillator; **CRT-P & CRT-D**: cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **MACE**: Composite of mortality, thoracic and cardiac complications, device-related infection and reoperation; **PPM**: permanent pacemaker.

Figure 4. Trends of in-hospital adverse events according to frailty group (2004-2014)*

* $p < 0.001$ for all trends except MACE in IRF ($p = 0.013$).

Figure 5. Adjusted relative risk (RR) and 95% confident intervals of adverse outcomes according to frailty risk group and type of CIED (reference is low-frailty risk group)

Legend:

* $p > 0.05$ ($p < 0.001$ otherwise); **Comp: complications; **ICD**: automated implantable cardioverter-defibrillator; **CRT-P & CRT-D**: cardiac resynchronization therapy - pacemaker and - defibrillator, respectively; **MACE**: Composite of mortality, thoracic and cardiac complications, device-related infection and reoperation; **PPM**: permanent pacemaker; models adjusted for: age, sex, weekend admission, primary expected payer, median household income, dyslipidemia, smoking status, previous acute myocardial infarction, previous coronary artery bypass grafting, history of ischemic heart disease, previous percutaneous coronary intervention, previous cerebrovascular accidents, family history of coronary artery disease, bed size of hospital, region of hospital, location/teaching status of hospital, year of admission, history of cardiac arrest, ventricular tachycardia and ventricular fibrillation, atrial fibrillation, acquired immune deficiency syndrome, rheumatoid arthritis/collagen vascular diseases, congestive heart failure, chronic pulmonary disease, coagulopathy, diabetes, hypertension, hypothyroidism, liver disease, lymphoma, metastatic cancer, other neurological disorders, obesity, peripheral vascular disorders, solid tumor without metastasis, valvular heart disease, and weight loss.

Table 1. In-hospital clinical outcomes of total cohort according to frailty risk group

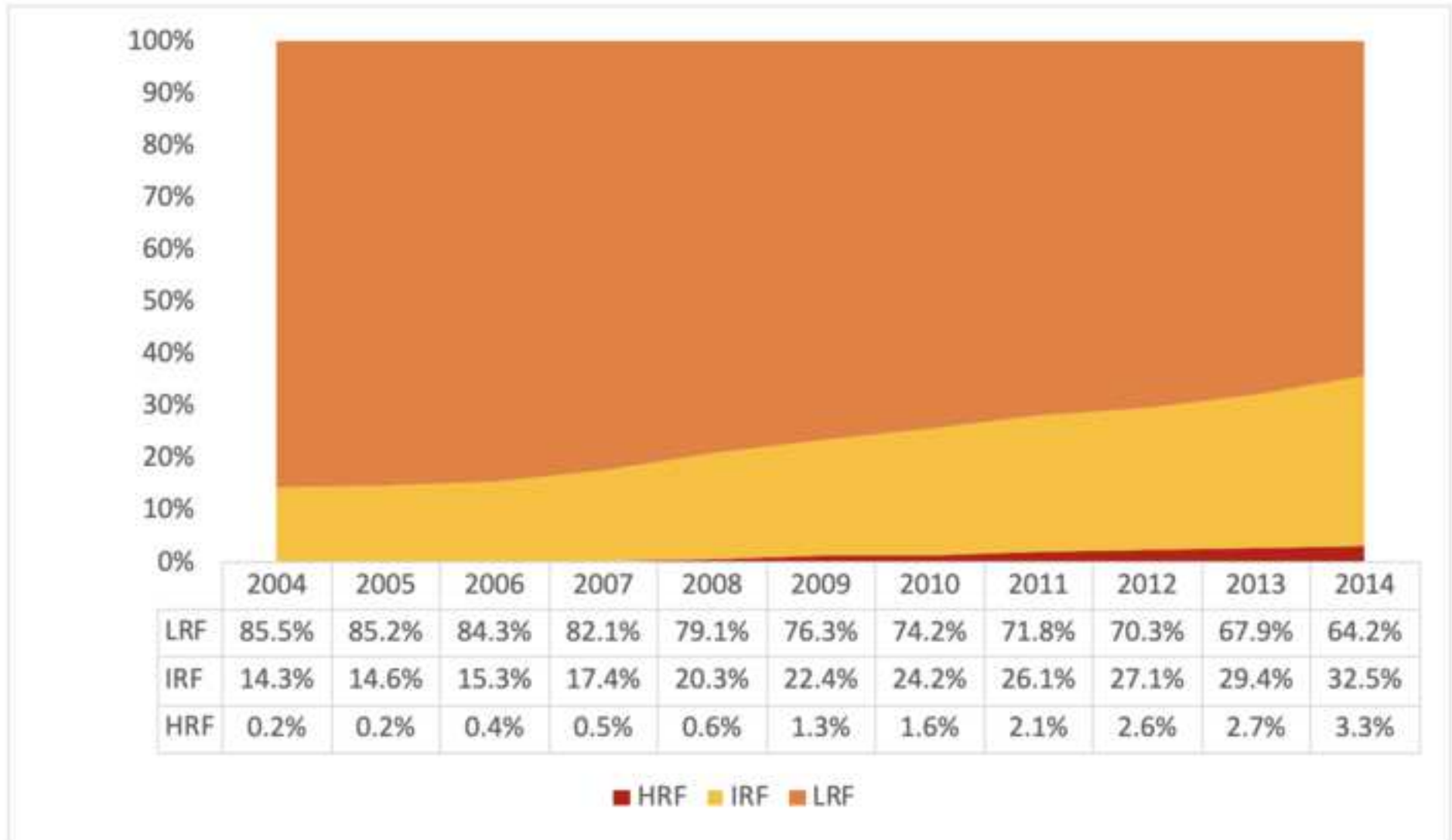
Variable/Frailty Risk (% of cohort)	LRF (77.6)	IRF (21.2)	HRF (1.2)	Total	p-value
MACE, %*	3.5	9.9	13.9	5.0	<0.001
All-cause mortality, %	0.4	2.9	5.3	1.0	<0.001
Procedure-related bleeding, %	2.0	6.0	8.7	2.9	<0.001
Thoracic complications, %	2.3	5.2	7.5	3.0	<0.001
Pneumothorax, %	1.7	4.4	6.7	2.3	<0.001
Hemothorax, %	0.0	0.0	0.1	0.0003	<0.001
Hemopericardium, %	0.0	0.1	0.1	0.1	<0.001
Cardiac tamponade, %	0.1	0.3	0.5	0.2	<0.001
Cardiac complications, %	0.3	0.7	0.7	0.4	<0.001
Device-related infection, %*	0.6	2.0	1.9	0.9	<0.001
Lead revision, %	1.6	1.5	1.4	1.6	0.003
Pocket revision, %	1.0	1.5	1.6	1.2	<0.001
Length of stay (days), median (IQR)	3 (1,6)	8 (5,13)	11 (7,19)	4 (2,7)	<0.001
Total charge (US Dollars), median (IQR)	66509 (39485, 110596)	92938 (53962, 164373)	120777 (69664, 223105)	71641 (42142, 120910)	<0.001

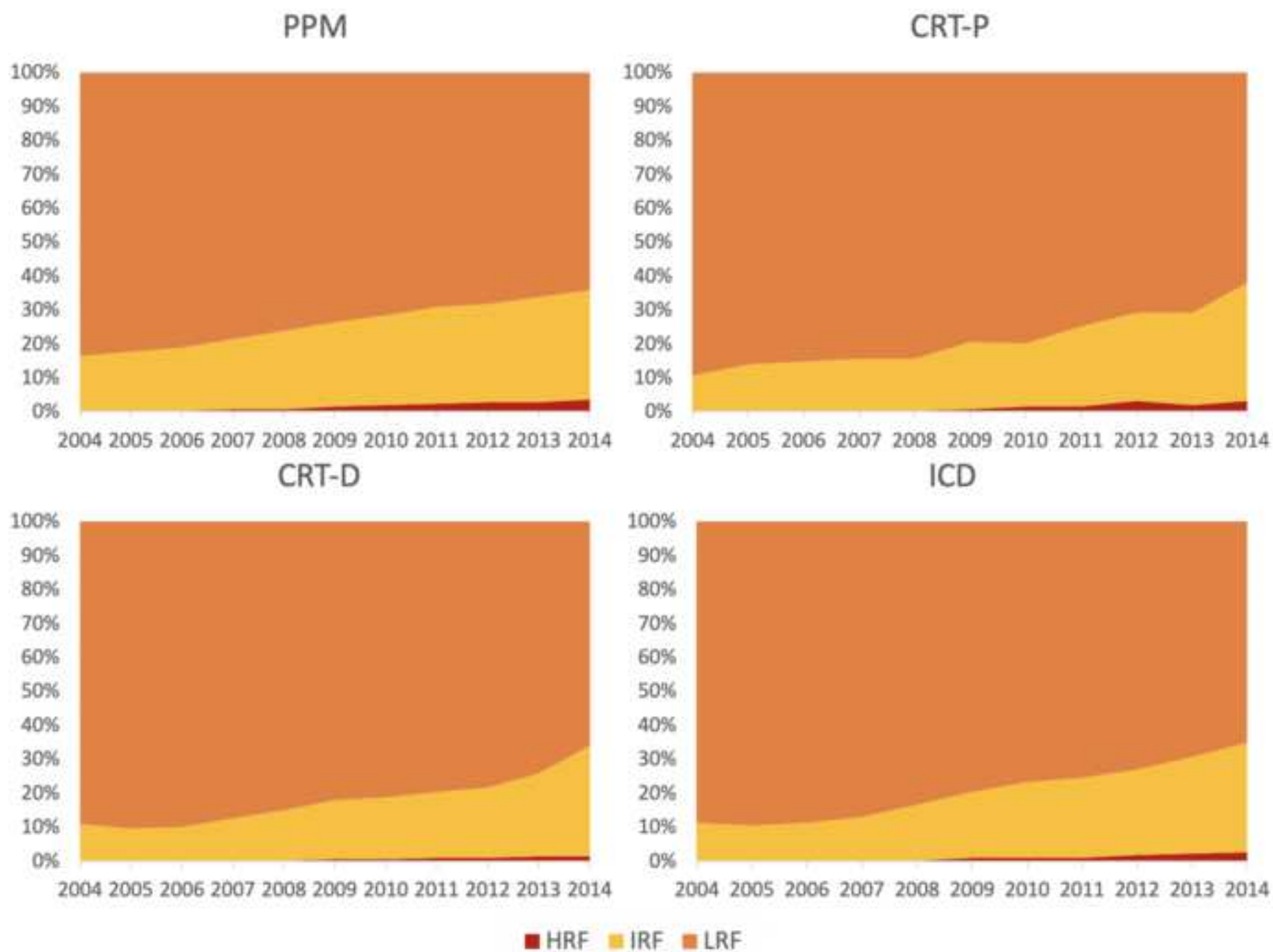
*MACE: Composite of mortality, thoracic and cardiac complications, device-related infection and reoperation; **HRF**: High-risk frailty; **IRF**: Intermediate-risk frailty; **LRF**: Low-risk frailty.

Table 2. Adjusted odds of adverse outcomes according to frailty risk level (indicator low frailty risk)

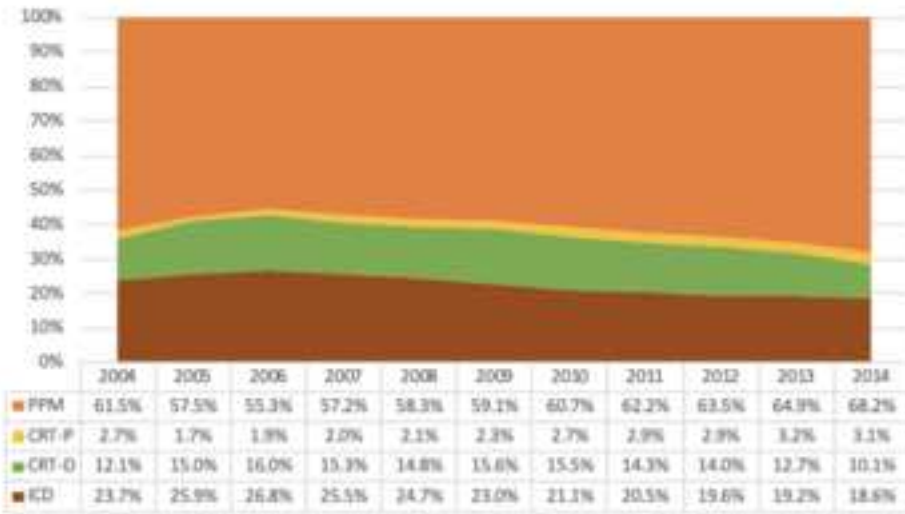
Frailty Risk Group/Outcome	MACE		Mortality		Procedure-related Bleeding		Thoracic Complications		Cardiac Complications	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	p-value
Total										
LRF (reference)	-	-	-	-	-	-	-	-	-	-
IRF	2.41 [2.38, 2.45]	<0.001	5.01 [4.85, 5.18]	<0.001	2.20 [2.16, 2.24]	<0.001	1.76 [1.73, 1.79]	<0.001	1.82 [1.74, 1.92]	<0.001
HRF	2.97 [2.87, 3.08]	<0.001	8.32 [7.82, 8.84]	<0.001	2.44 [2.33, 2.55]	<0.001	2.01 [1.92, 2.11]	<0.001	1.52 [1.32, 1.75]	<0.001
PPM										
LRF (reference)	-	-	-	-	-	-	-	-	-	-
IRF	2.20 [2.17, 2.24]	<0.001	4.67 [4.49, 4.85]	<0.001	2.09 [2.05, 2.14]	<0.001	1.64 [1.60, 1.67]	<0.001	1.89 [1.77, 2.00]	<0.001
HRF	2.79 [2.67, 2.90]	<0.001	8.18 [7.63, 8.77]	<0.001	2.48 [2.35, 2.60]	<0.001	1.93 [1.83, 2.04]	<0.001	1.72 [1.47, 2.01]	<0.001
CRT-P										
LRF (reference)	-	-	-	-	-	-	-	-	-	-
IRF	2.96 [2.74, 3.20]	<0.001	4.81 [4.00, 5.78]	<0.001	2.84 [2.54, 3.17]	<0.001	2.16 [1.96, 2.38]	<0.001	4.39 [3.33, 5.79]	<0.001
HRF	3.59 [2.96, 4.36]	<0.001	8.57 [5.87, 12.50]	<0.001	3.88 [3.03, 4.95]	<0.001	2.24 [1.76, 2.86]	<0.001	3.78 [1.81, 7.87]	<0.001
CRT-D										
LRF (reference)	-	-	-	-	-	-	-	-	-	-
IRF	3.07 [2.95, 3.19]	<0.001	6.83 [6.16, 7.58]	<0.001	2.78 [2.61, 2.95]	<0.001	2.08 [1.97, 2.19]	<0.001	1.55 [1.32, 1.81]	<0.001
HRF	3.00 [2.62, 3.43]	<0.001	7.06 [5.41, 9.21]	<0.001	2.45 [2.02, 2.97]	<0.001	1.67 [1.37, 2.03]	<0.001	1.34 [0.77, 2.32]	0.303
ICD										
LRF (reference)	-	-	-	-	-	-	-	-	-	-
IRF	2.71 [2.62, 2.80]	<0.001	5.97 [5.45, 6.54]	<0.001	2.16 [2.06, 2.26]	<0.001	1.95 [1.87, 2.04]	<0.001	1.57 [1.41, 1.76]	<0.001
HRF	3.53 [3.21, 3.87]	<0.001	9.07 [7.51, 10.95]	<0.001	1.75 [1.53, 1.99]	<0.001	2.54 [2.26, 2.87]	<0.001	1.12 [0.98, 1.21]	0.07

ICD: automated implantable cardioverter-defibrillator; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **PPM:** permanent pacemaker; **MACE:** Composite of mortality, thoracic and cardiac complications, device-related infection and reoperation; **HRF:** High-risk frailty; **IRF:** Intermediate-risk frailty; **LRF:** Low-risk frailty.

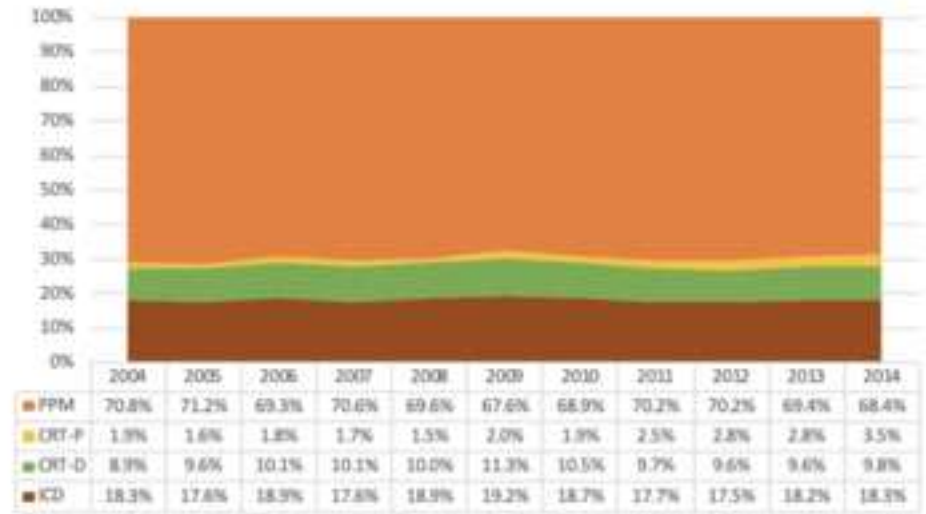




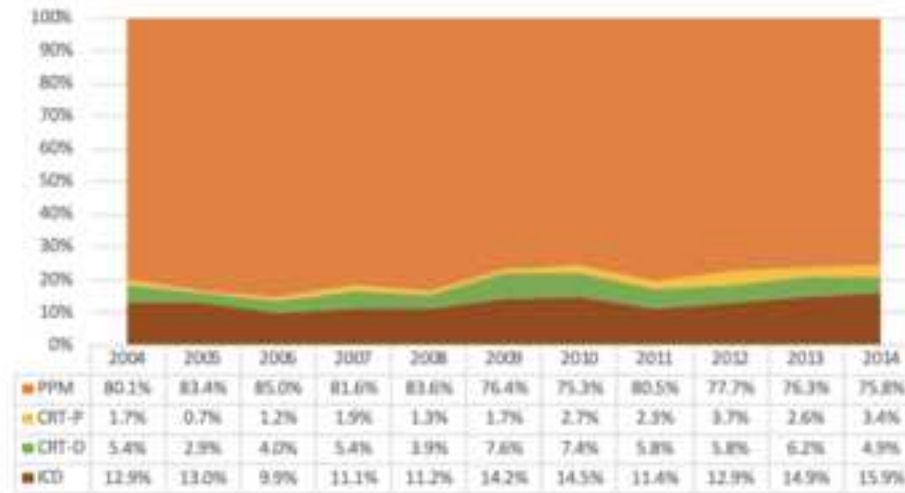
LRF



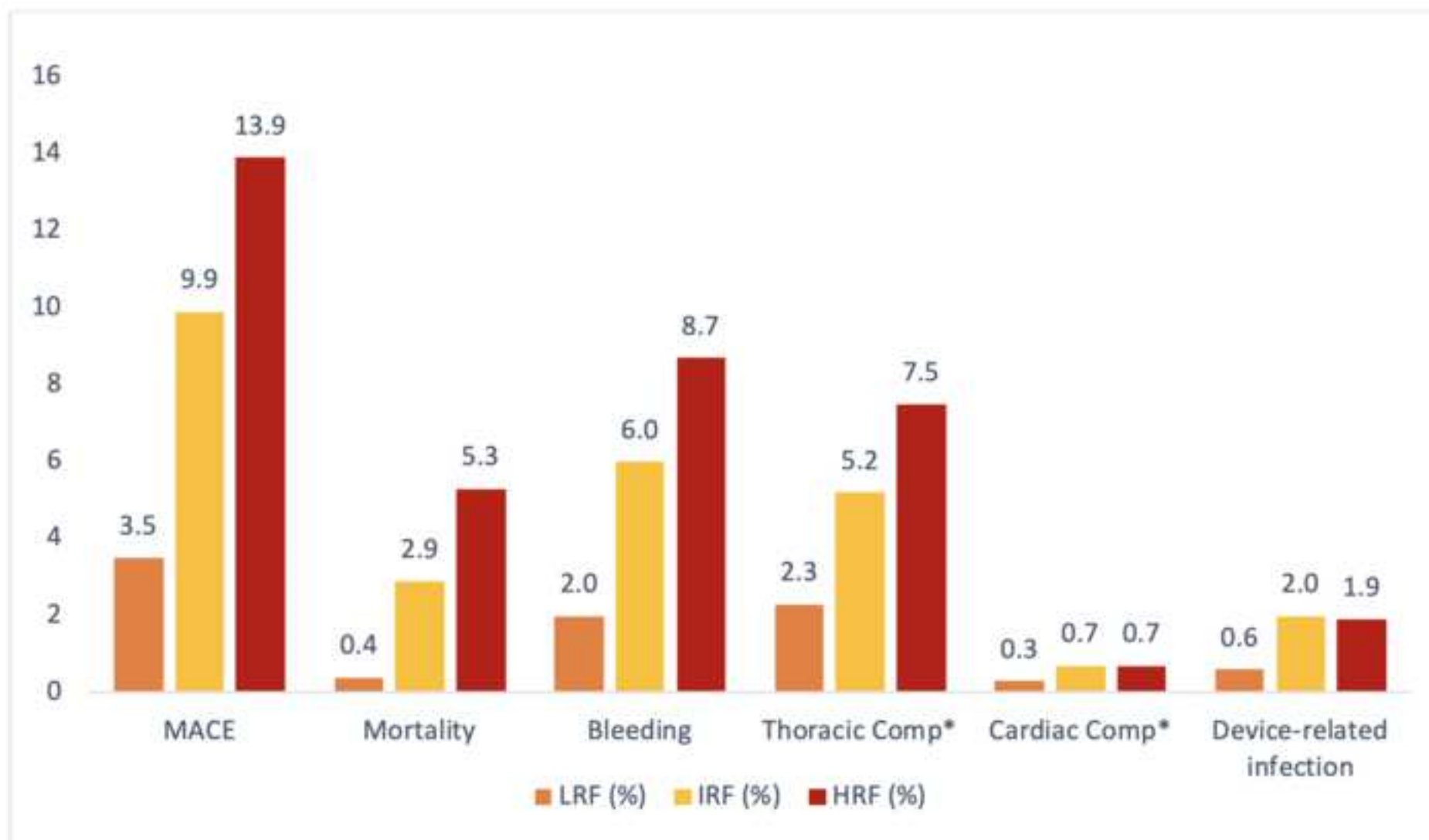
IRF



HRF



- ICD
- CRT-D
- CRT-P
- PPM



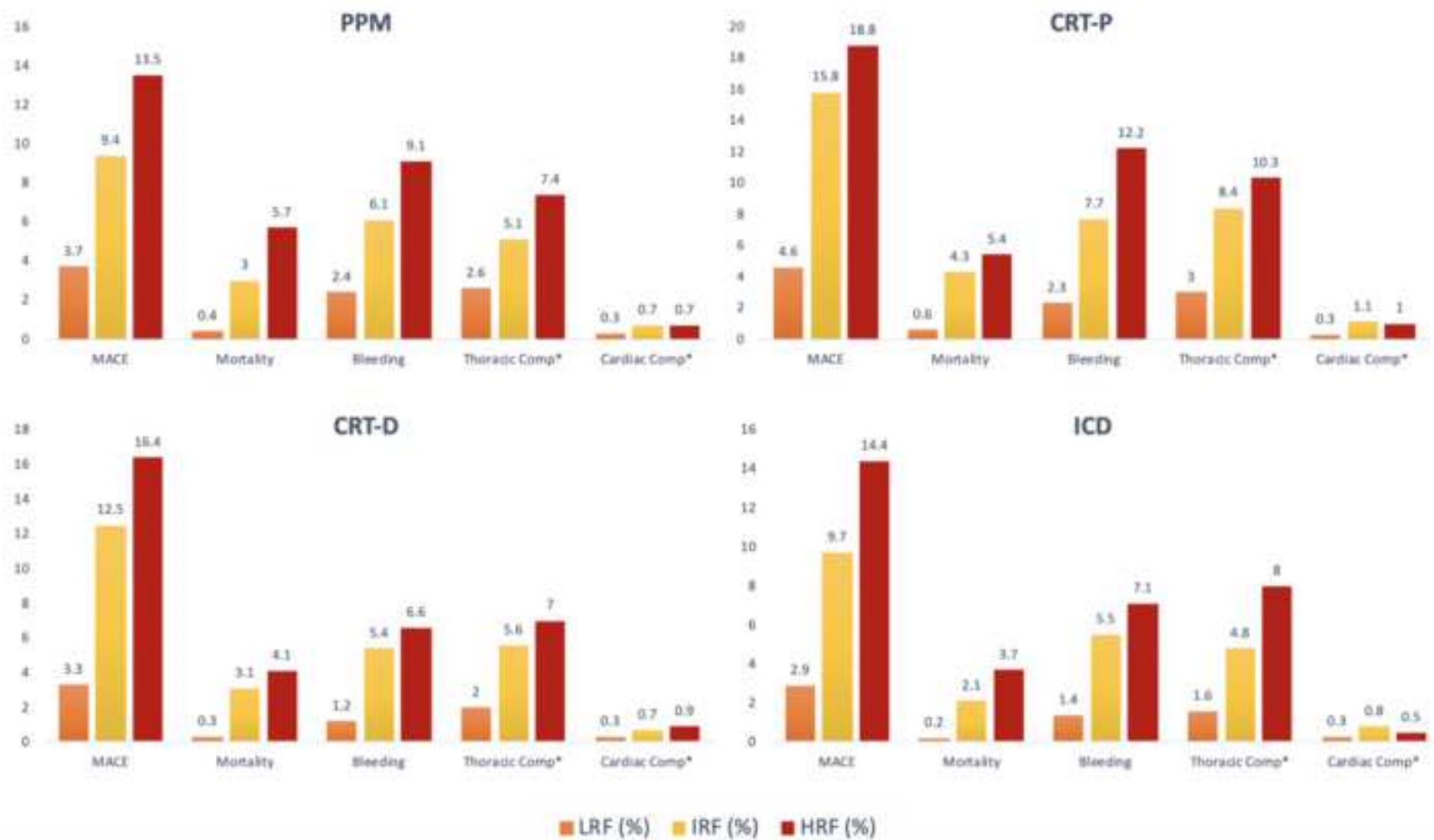
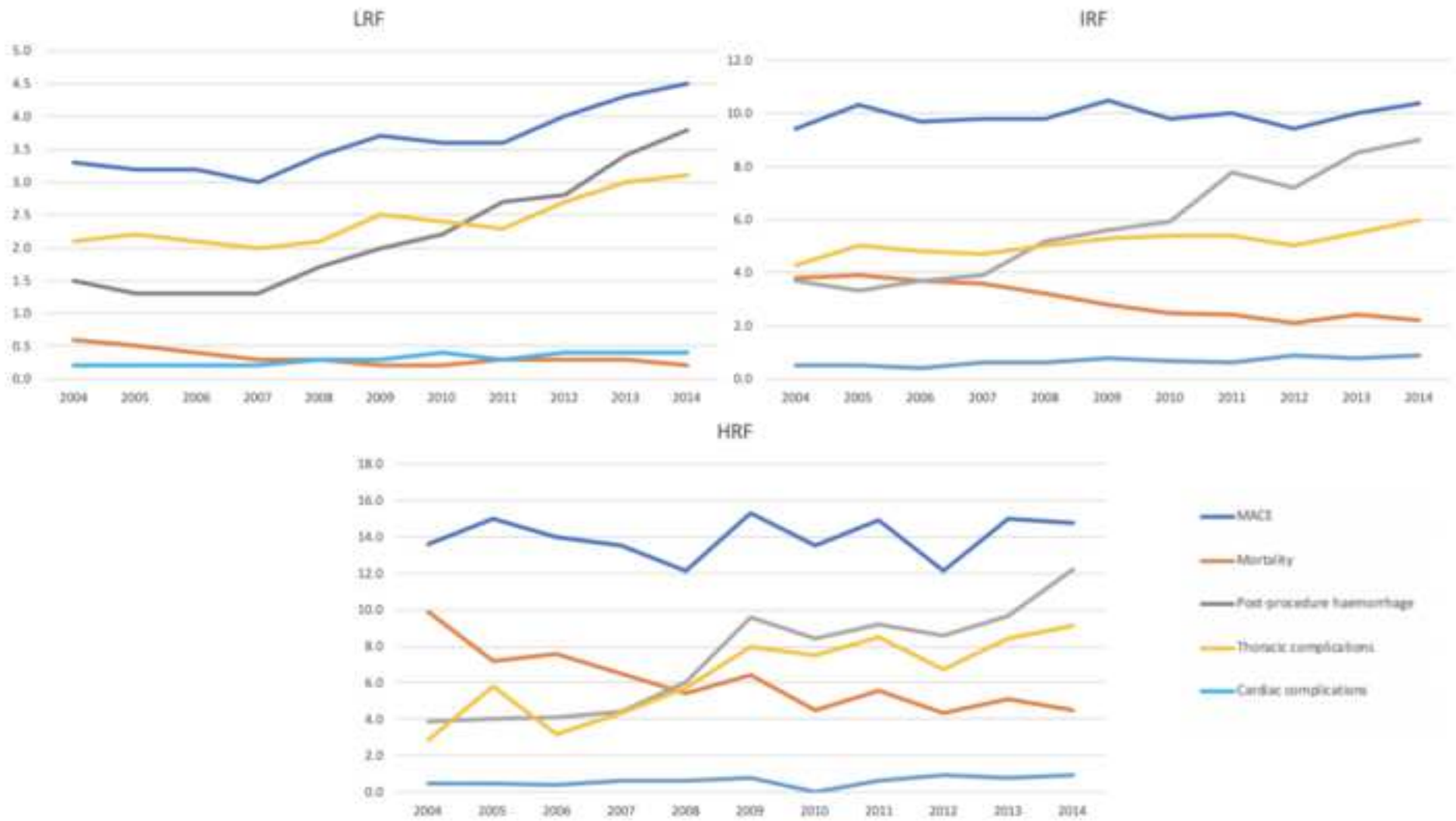
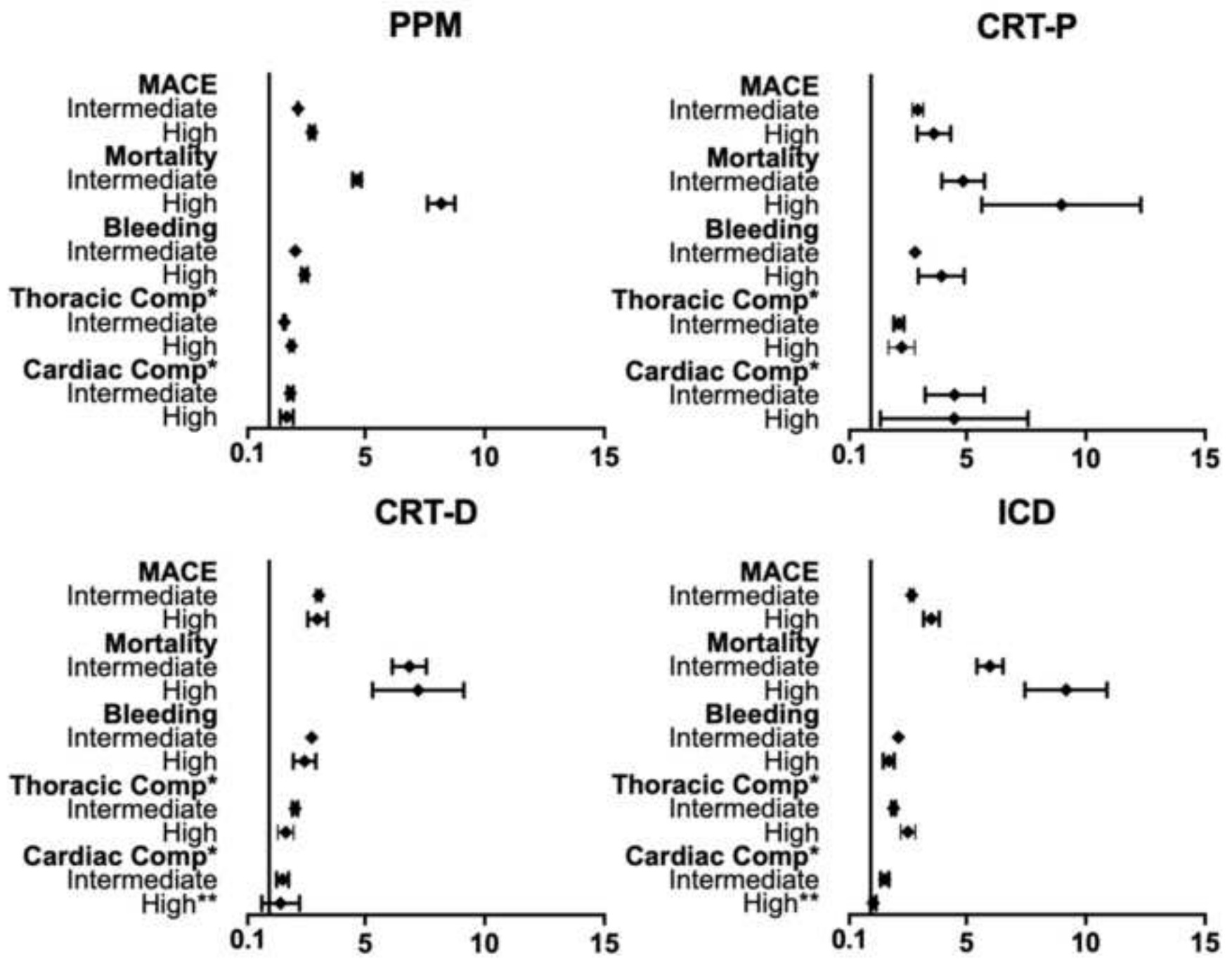
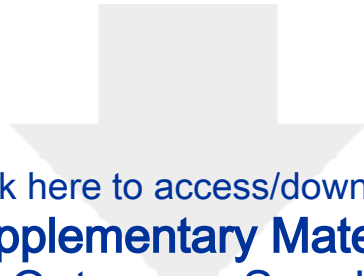


Figure 4







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