Canadian Journal of Cardiology 35 (2019) 1465–1474

Clinical Research

Prevalence, Outcomes, and Costs According to Patient Frailty Status for 2.9 Million Cardiac Electronic Device Implantations in the United States

Mohamed O. Mohamed, MRCP(UK),[a,b] Parikshit S. Sharma, MD, MPH,[c] Annabelle S. Volgman, MD,[c] Rahul Bhardwaj, MD,[d] Chun Shing Kwok, MRCP(UK),[a,b] Muhammad Rashid, MRCP(UK),[a] Diane Barker, MD,[b] Ashish Patwala, MD,[b] and Mamas A. Mamas, DPhil[a,b,e]

[a] *Keele Cardiovascular Research Group, Centre for Prognosis Research, Institutes of Applied Clinical Science and Primary Care and Health Sciences, Keele University, Keele, United Kingdom*

[b] *Department of Cardiology, Royal Stoke University Hospital, Stoke-on-Trent, United Kingdom*

[c] *Department of Medicine, Section of Cardiology, Rush University Medical Center, Chicago, Illinois, USA*

[d] *Loma Linda University, Loma Linda, California, USA*

[e] *Institute of Population Sciences, University of Manchester, Manchester, United Kingdom*

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: 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- to 3-fold higher in the IRF and HRF groups, whereas all-cause mortality was 4- to 9-fold higher in the IRF (2.9%) and HRF (5.3%) groups, depending on the type of CIED ($P < 0.001$ for all). Rates of complications

RÉSUMÉ

Contexte : On en sait très peu au sujet de l'incidence de la fragilité du patient sur la durée de l'hospitalisation, le coût et les résultats de l'intervention en milieu hospitalier associés à la pose d'un dispositif cardiaque électronique implantable (DCEI).

Méthodologie : Toutes les implantations *de novo* d'un DCEI consignées entre 2004 et 2014 dans une base de données nationale aux États-Unis ont été stratifiées en trois groupes en fonction du score HFRS (*Hospital Frailty Risk Score*, score du risque de fragilité associé à l'hospitalisation) comme suit : risque de fragilité faible (RFF; < 5), intermédiaire (RFI; 5-15) ou élevé (RFE; < 15). L'association entre la fragilité et les résultats des interventions a été évaluée au moyen d'analyses de régression.

Résultats : Pour l'ensemble des 2 902 721 implantations réalisées, le RFF, le RFI et le RFE s'établissaient respectivement à 77,6 %, 21,2 % et 1,2 %. La fragilité des patients a augmenté entre 2004 et 2014; le

The association between frailty and cardiovascular outcomes has become increasingly recognized in recent years.[1-3] 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, whereas 25% of frail individuals have only 1 chronic condition.[5]

Cardiac implantable electronic devices (CIEDs), including permanent pacemakers (PPM) and implantable cardioverter-

Received for publication June 6, 2019. Accepted July 30, 2019.

Corresponding author: Dr Mamas A. Mamas, Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute for Primary Care and Health Sciences, Keele University, University Drive, Keele ST5 5BG, United Kingdom.

E-mail: mamasmamas1@yahoo.co.uk

See page 1474 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.07.632

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

Conclusions: 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.

RFI est passé de 14,3 % à 32,5 % et le RFE, de 0,2 % à 3,3 %. Les complications étaient de 2 à 3 fois plus élevées dans les groupes exposés à un RFI ou à un RFE, tandis que la mortalité toutes causes confondues était de 4 à 9 fois plus élevée dans les groupes exposés à un RFI (2,9 %) ou à un RFE (5,3 %), selon le type de DCEI ($p < 0,001$ dans les deux cas). Les taux de complications ont augmenté au fil de la période visée par l'étude, alors que la mortalité toutes causes confondues a diminué, en particulier dans les groupes exposés à un risque de fragilité supérieur (2004 vs 2014; mortalité : RFI, 3,8 % vs 2,2 %; RFE, 9,9 % vs 4,5 %; hémorragie : RFI, 3,7 % vs 9,0 %; RFE, 3,9 % vs 12,2 %; complications thoraciques : RFI, 4,3 % vs 6,0 %; RFE, 2,9 % vs 9,1 %; complications cardiaques : RFI, 0,5 % vs 0,9 %; RFE, 0,5 % vs 0,9 %). L'augmentation de la fragilité des patients a été associée à une hausse du coût ($p < 0,001$) et de la durée de l'hospitalisation (médiane de 3, 8 et 11 jours pour le RFF, le RFI et le RFE, respectivement; $p < 0,001$). Le coût de la pose d'un défibrillateur chez des patients présentant un RFE s'établissait à environ un quart de million de dollars US par patient.

Conclusions : La fragilité est associée à de moins bons résultats cliniques, à un coût supérieur et à une hospitalisation plus longue, quel que soit l'âge du patient ou le type de DCEI. Les résultats de l'étude font ressortir l'importance d'évaluer la fragilité des patients.

defibrillators (ICD), are important in the management of serious rhythm abnormalities. CIEDs also include cardiac resynchronization therapy with a pacemaker alone (CRT-P) or with a 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 have 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,[3,11,12] but these have been limited by their analyses of specific types of CIED procedures (eg, ICD) in patients with certain indications (eg, primary prevention) or in highly specialized centres, 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,[2,3,13] while excluding younger and comorbid patients who may be biologically frail.[7]

Although numerous frailty scores exist, no single score is considered a gold standard.[14] 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 data,[15] and was validated against 2 prominent scores: Fried Frailty Phenotype and Rockwood Frailty Index. In the present study, we used the HFRS to study trends in frailty in the United States over a 10-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.[16] Further information on its structure and validation is available in Supplemental Appendix S1.

Study design and population

All hospitalizations during which *de novo* CIED implantations were performed were retrospectively analysed. 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 Supplemental 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 3 risk groups: low-risk frailty (LRF; < 5), intermediate-risk frailty (IRF; 5-15), and high-risk frailty (HRF; > 15) (Supplemental 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 Supplemental 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 diagnosis and procedure codes (see Supplemental Table S1): procedure-related bleeding, cardiac complications, and thoracic complications.

Outcomes

The primary outcome measures were in-hospital rates of all-cause mortality, major adverse cardiovascular events (MACE), and procedural-related complications (bleeding, thoracic, and cardiac complications) between frailty risk groups according to the 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 haemorrhage according to ICD-9 diagnosis codes specified in Supplemental 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, haemopericardium, pericardiocentesis.

The secondary outcome was to evaluate the economic burden of CIED implantations in patients with intermediate and high risk of frailty compared with 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 and were compared using the Kruskal-Wallis test. Categorical variables are presented as percentages and were analysed using the χ^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 LRF as the reference category in the form of adjusted odds ratios (aOR), and adjusting for all covariates that were not part of the HFRS as mentioned in Supplemental Appendix S2). The model fits were assessed using the Hosmer-Lemeshow statistic,[17] 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 (> or <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 the 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 CIEDs (Fig. 1B). The most common procedure in all study groups was PPM insertion, followed by ICD, CRT-D, and finally CRT-P (Supplemental Table S3). There was a shifting trend towards more complex device implantations in patients with HRF over the study period (Fig. 1C).

Several differences in patient demographics are observed between the frailty risk groups of the entire CIED cohort (Supplemental 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, hypertension, and valvular heart disease, they were less likely to have had a history of acute myocardial infarction or have undergone previous percutaneous coronary intervention or coronary artery bypass grafting. The demographic differences between frailty risk groups were also similar in the subgroup analyses of individual devices (PPM, CRT-P, CRT-D, and ICD; Supplemental Tables S4-S6).

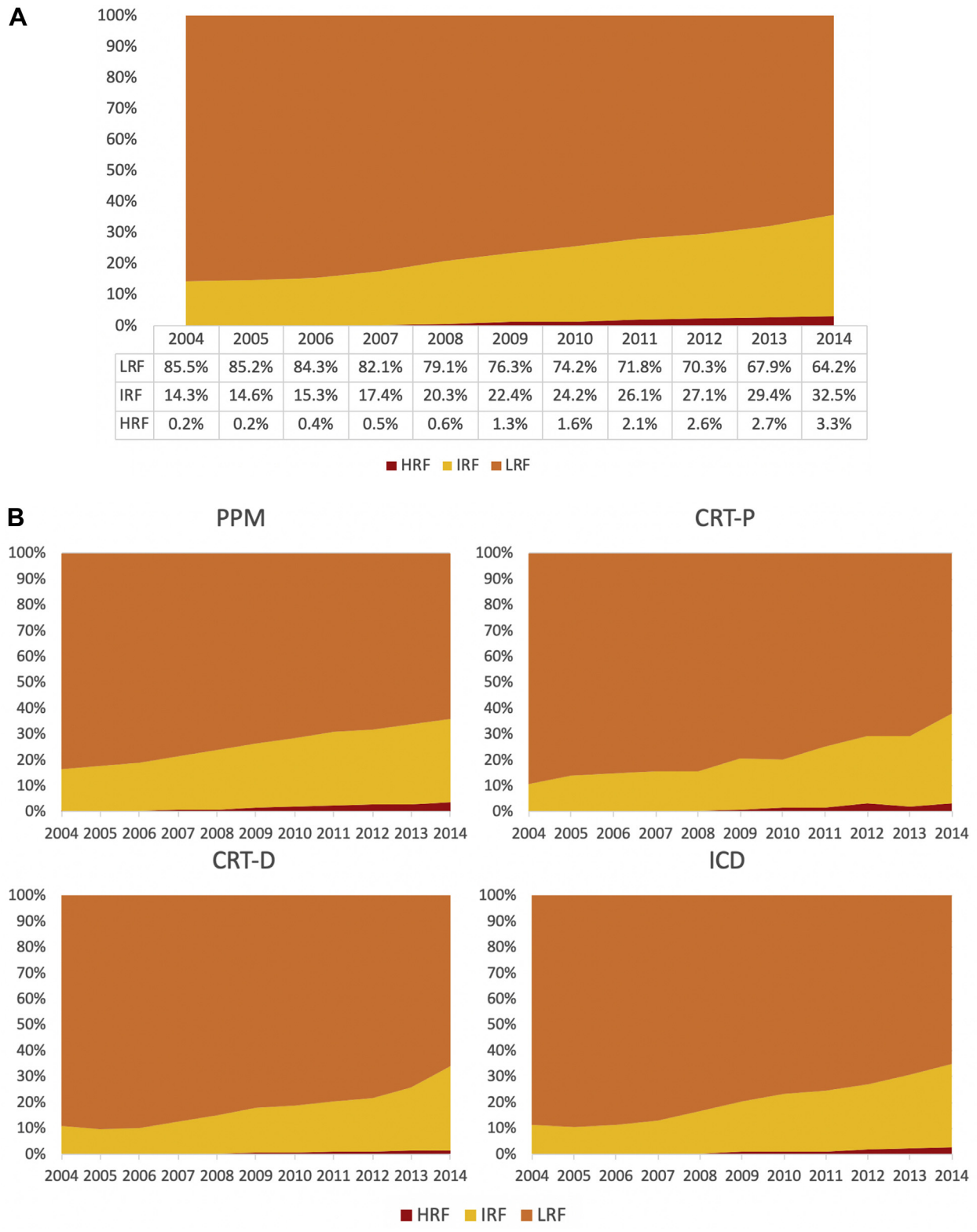
In-hospital adverse outcomes

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, Fig. 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 with 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, Fig. 2) as well as in each CIED subgroup (see Supplemental Table S7, Fig. 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 2- to 3-fold (IRF and HRF, Fig. 4, Supplemental Table S8). In contrast, all-cause mortality has decreased over the study years, particularly in the higher risk groups (IRF and HRF, Fig. 4, Supplemental Table S8).

Device-related infection was more than 3-fold higher in the IRF and HRF groups compared with 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, Fig. 2). The higher risk of device-related infection in both IRF and HRF groups was consistent across all CIED subtypes compared with the LRF group, but was exceptionally higher in frail patients (IRF and HRF) undergoing complex device implantation (CRT-D, CRT-P, and ICD) compared with those undergoing pacemakers (Supplemental Table S7, Fig. 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 with 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 2- to 3-fold higher in the IRF and HRF groups compared with the LRF group, regardless of the type of implanted device (Table 2, Fig. 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 with



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
LRF	85.5%	85.2%	84.3%	82.1%	79.1%	76.3%	74.2%	71.8%	70.3%	67.9%	64.2%
IRF	14.3%	14.6%	15.3%	17.4%	20.3%	22.4%	24.2%	26.1%	27.1%	29.4%	32.5%
HRF	0.2%	0.2%	0.4%	0.5%	0.6%	1.3%	1.6%	2.1%	2.6%	2.7%	3.3%

Figure 1. (**A**) Prevalence of frailty amongst patients undergoing cardiac implantable electronic device (CIED) implantations (2004-2014). (**B**) Prevalence of frailty according to the type of CIED (2004-2014). (**C**) Proportion of CIEDs utilized according to frailty group (2004-2014). CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; HRF, high-risk frailty; ICD, implantable cardioverter-defibrillator; IRF, intermediate-risk frailty; LRF, low-risk frailty; PPM, permanent pacemaker.

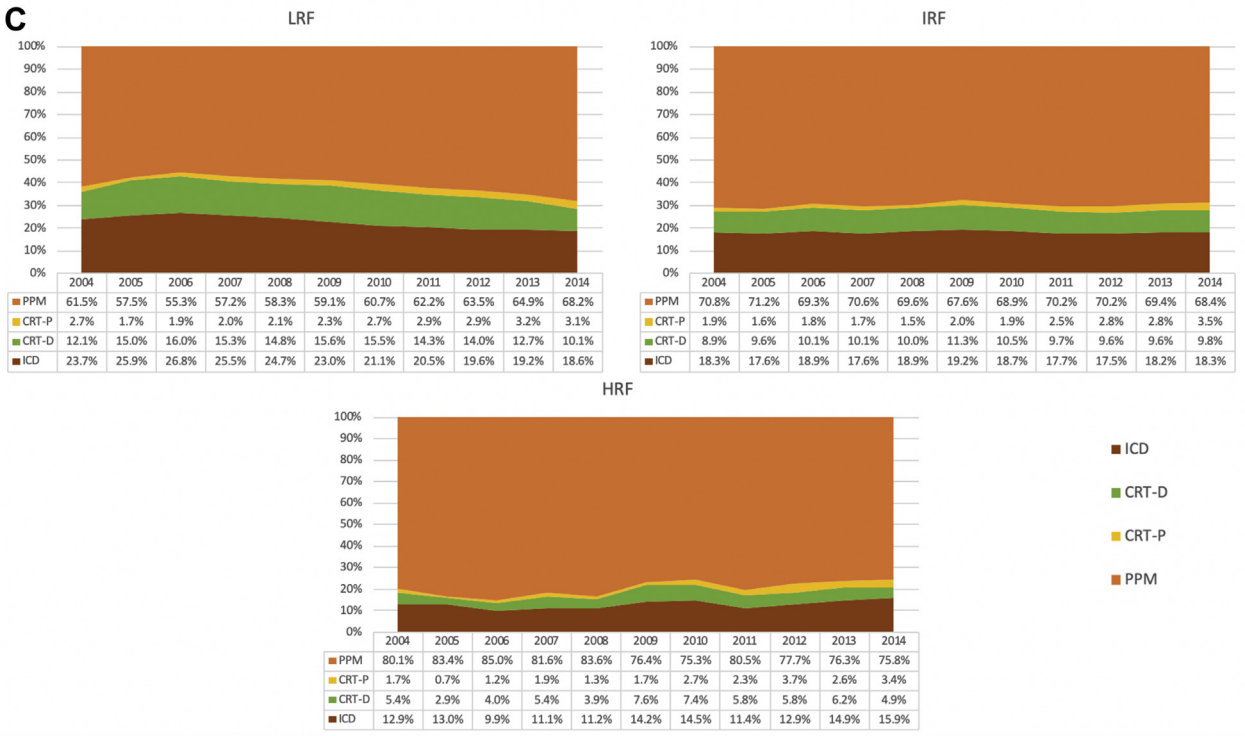


Figure 1. (*continued*).

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 7-fold increased odds of all-cause mortality compared with 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 ($\geq$ 1.5-fold) in patients with IRF and HRF when compared with the LRF group (Fig. 5), with the exception of cardiac complications in patients undergoing CRT-P implantation (4-fold increased odds in the IRF and HRF groups) and ICD (insignificant odds in patients with HRF: 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 Supplemental 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 Supplemental Table S7). Median hospitalization charges were approximately 1.5- and 2-fold higher in the IRF and HRF groups, respectively, compared with the LRF group, in all CIED subtypes (Supplemental Table S7).

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

Sensitivity analysis

A sensitivity analysis of clinical outcomes stratified by patient age (< or > 75 years) was performed (Supplemental Table S10). The proportion of patients younger than 75 years at the time of CIED implantation was 48% (n = 1,351,900). At least 1 in 6 young patients (< 75 years; 17.4%) was classified as IRF, and 0.8% of young patients were HRF.

All adverse events were higher in the IRF and HRF groups in both young and old patients (Supplemental 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 patients with IRF and HRF from 14.3% to 32.5% and 0.2% to 3.3%, respectively, between 2004 and 2014. Patients with IRF and HRF compared with those with LRF, 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 health care facilities where patients undergo CIED implantation procedures where the length of stay and

Table 1. In-hospital clinical outcomes of the total cohort according to the 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
Haemothorax, %	0.0	0.0	0.1	0.0003	< 0.001
Haemopericardium, %	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 (d), median (IQR)	3 (1, 6)	8 (5, 13)	11 (7, 19)	4 (2, 7)	< 0.001
Total charge (USD$), median (IQR)	66,509 (39,485, 110,596)	92,938 (53,962, 164,373)	120, 777 (69,664, 223,105)	71,641 (42,142, 120,910)	< 0.001

HRF, high-risk frailty; IQR, interquartile range; IRF, intermediate-risk frailty; LRF, low-risk frailty.
*MACE, composite of mortality, thoracic and cardiac complications, device-related infection, and reoperation.

hospitalization charges of patients with IRF and HRF were notably higher than in patients with LRF.

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 patients with IRF and HRF receiving such procedures over the study period. A European Heart Rhythm Association survey recently showed that less than 10% of patients undergoing CIED implantations in European centres are considered prefrail or frail.[13] 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.[18] reported a frailty prevalence of 12.8% amongst patients with CIEDs implanted more than 2 months before attending an ambulatory device clinic in a tertiary centre in the United States, although their inclusion cohort (n = 219) represented less than half of patients who attended their ambulatory device clinic (n = 448).

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. All-cause in-hospital mortality in patients with IRF and HRF was 5- to 9-fold higher than that in patients with LRF, depending on the type of CIED implanted, whereas other complications were between 50% and 150% more likely to occur in patients with IRF and HRF 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 HRF. The observed upward trend in complications is in line with more complex device implantations, whereas the decline in mortality is likely due to advancements in specialized geriatric care provided to more frail patients or better case selection.[19] A study of Medicare patients with heart failure undergoing primary prevention ICD implantation between 2006 and 2009 reported significantly higher 1-year mortality in frail patients compared with those without any medical

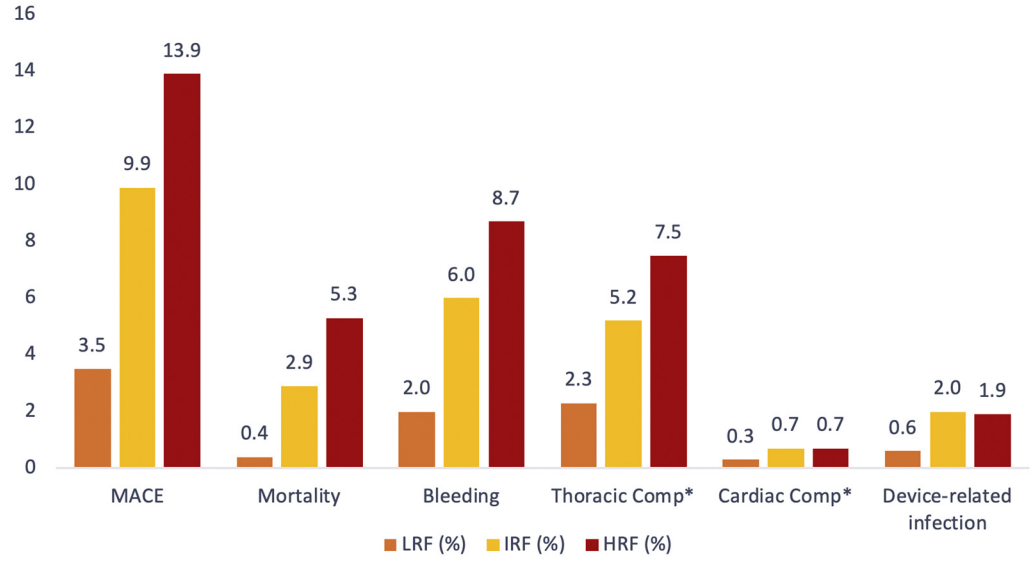


Figure 2. In-hospital adverse events of frailty groups in the total cohort. HRF, high-risk frailty; IRF, intermediate-risk frailty; LRF, low-risk frailty; MACE, composite of mortality, thoracic and cardiac complications, device-related infection, and reoperation. *Comp: complications; $P < 0.001$ for all outcomes.

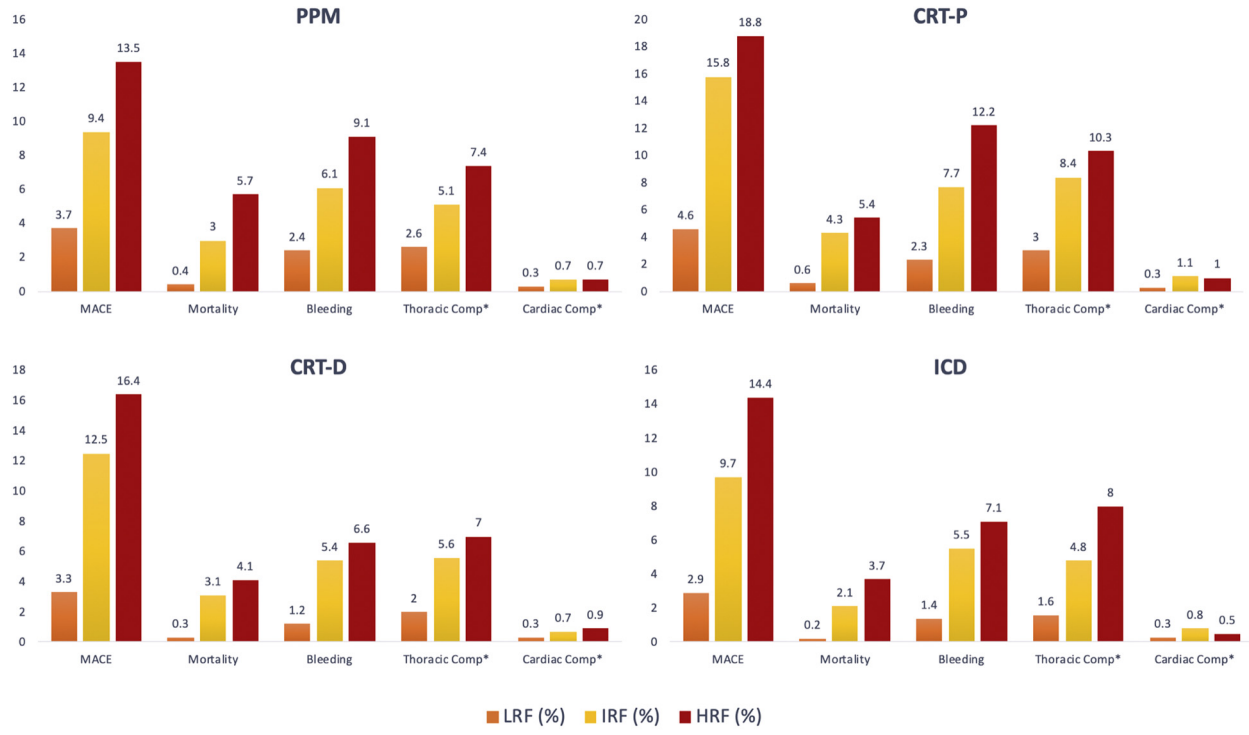


Figure 3. In-hospital adverse events in frailty groups according to the type of cardiac implantable electronic device. CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; HRF, high-risk frailty; ICD, implantable cardioverter-defibrillator; IRF, intermediate-risk frailty; LRF, low-risk frailty; MACE, composite of mortality, thoracic and cardiac complications, device-related infection, and reoperation; PPM, permanent pacemaker. *Comp: complications; $P < 0.001$ for all outcomes.

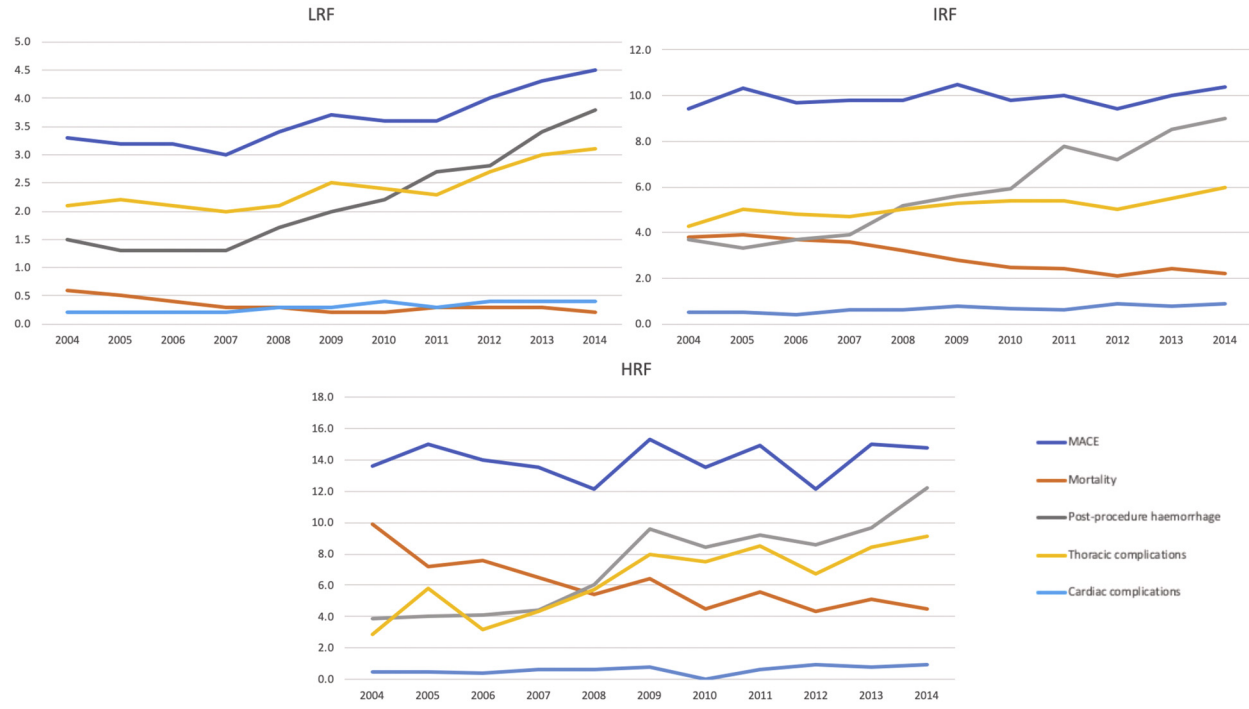


Figure 4. Trends of in-hospital adverse events according to the frailty group (2004-2014). HRF, high-risk frailty; IRF, intermediate-risk frailty; LRF, low-risk frailty; MACE, composite of mortality, thoracic and cardiac complications, device-related infection, and reoperation. $P < 0.001$ for all trends except MACE in IRF ($P = 0.013$).

Table 2. Adjusted odds of adverse outcomes according to the 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

CI, confidence interval; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy—pacemaker; HRF, high-risk frailty; ICD, implantable cardioverter-defibrillator; IRF, intermediate-risk frailty; LRF, low-risk frailty; MACE, composite of mortality, thoracic and cardiac complications, device-related infection, and reoperation; OR, odds ratio; PPM, permanent pacemaker.

conditions other than heart failure (22% vs 4%).[3] Although their analysis provided insight into 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.[20] 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 nondefibrillator (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 who are currently much less likely to receive a defibrillator device according to a recent European Heart Rhythm Association survey.[13] 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 with the low frailty group, an observation that was consistent across all CIED subtypes. It is noteworthy that there rates of device-related infection were significantly higher in patients with IRF and HRF undergoing complex device therapy (CRT-P, CRT-D, and ICD; 2.6% to 5.3%) compared with those undergoing pacemaker implantation (1.4%). Although 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 patients with HRF. 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.[21,22] More frail patients are more susceptible to such processes due to their reduced host defense and resistance to infections.[11,12] Our present findings emphasize the importance of frailty assessment from an economic perspective because 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% to 100%) in patients with IRF and HRF, with an incremental rise in costs as the risk of frailty increases. Hospitalizations where patients with HRF received CRT-D and ICD devices cost almost a quarter million USD$ per

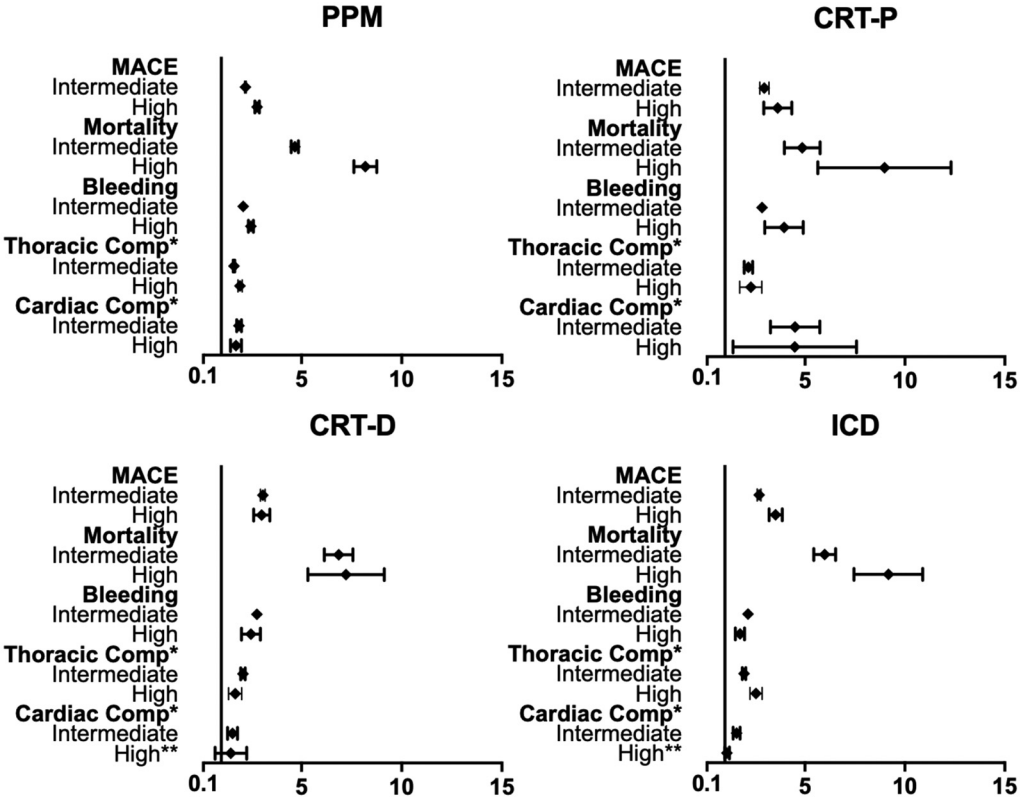


Figure 5. Adjusted relative risk and 95% confident intervals of adverse outcomes according to the frailty risk group and the type of cardiac implantable electronic device (reference is the low-frailty risk group). CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ICD, implantable cardioverter-defibrillator; 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 neurologic disorders, obesity, peripheral vascular disorders, solid tumour without metastasis, valvular heart disease, and weight loss. *$P > 0.05$ ($P < 0.001$ otherwise). **Comp: complications.

patient. This could be possibly attributed to the higher rate of complications in higher risk (IRF and HRF) groups that often require prolonged and more intensive management as evidenced by a longer length of stay (2- to 3-fold longer in patients with IRF and HRF compared with patients with LRF). These findings raise questions about the sustainability of offering such devices to frail patients, most of whom receive 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. Although prehabilitation in patients with frailty has been shown to improve outcomes in patients undergoing some procedures,[25] it is unclear whether targeting frailty in patients who are likely 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, because the NIS dataset does not provide information on pharmacotherapy, indication for each CIED device (eg, type of arrhythmia and primary vs secondary prevention in CRT-D and ICD procedures), type of pacemaker (dual chamber vs biventricular pacemaker), operator experience, and procedure time, we were unable to adjust for the differences in these covariates between the study groups. Third, the HFRS was validated in patients over the age of 75 years; however, our sensitivity analysis demonstrated similar outcomes between younger (< 75 years) and older (> 75 years) patients. Fourth, because 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 periprocedural and early postprocedural phase.

Conclusions

The present nationwide analysis of CIED implantations in the United States shows that IRF and HRF, 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 postprocedural 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.

Funding Sources

Dr Mohamed Mohamed receives PhD funding from Medtronic Ltd. Medtronic Ltd. was not involved in the conceptualization, design, conduct, analysis, or interpretation of the current study.

Disclosures

D. Barker is paid by Medtronic for educational sessions. The other authors have no conflicts of interest to disclose.

References

1. Finn M, Green P. The influence of frailty on outcomes in cardiovascular disease. Rev Esp Cardiol (Engl Ed) 2015;68:653-6.
2. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. J Am Coll Cardiol 2014;63:747-62.
3. Green AR, Leff B, Wang Y, et al. Geriatric conditions in patients undergoing defibrillator implantation for prevention of sudden cardiac death: prevalence and impact on mortality. Circ Cardiovasc Qual Outcomes 2016;9:23-30.
4. Xue Q-L. The frailty syndrome: definition and natural history. Clin Geriatr Med 2011;27:1-15.
5. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.
6. Schuurmans H, Steverink N, Lindenberg S, Frieswijk N, Slaets JPJ. Old or frail: what tells us more? J Gerontol A Biol Sci Med Sci 2004;59:M962-5.
7. Bagshaw M, Majumdar SR, Rolfson DB, et al. A prospective multicenter cohort study of frailty in younger critically ill patients. Crit Care 2016;20:175.
8. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 2013;34:2281-329.
9. Parkash R, Sapp J, Gardner M, et al. Use of administrative data to monitor cardiac implantable electronic device complications. Can J Cardiol 2019;35:100-3.
10. Bennett M, Parkash R, Nery P, et al. Canadian Cardiovascular Society/Canadian Heart Rhythm Society 2016 Implantable Cardioverter-Defibrillator Guidelines. Can J Cardiol 2017;33:174-88.
11. Uslan DZ, Baddour LM. Cardiac device infections: getting to the heart of the matter. Curr Opin Infect Dis 2006;19:345-8.
12. Jones SR. Infections in frail and vulnerable elderly patients. Am J Med 1990;88:30S-3S. discussion 38S-42S.
13. Fumagalli S, Potpara TS, Bjerregaard Larsen T, et al. Frailty syndrome: an emerging clinical problem in the everyday management of clinical arrhythmias. The results of the European Heart Rhythm Association survey. Europace 2017;19:1896-902.
14. Aguayo GA, Donneau AF, Vaillant MT, et al. Agreement between 35 published frailty scores in the general population. Am J Epidemiol 2017;186:420-34.
15. Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. Lancet 2018;391:1775-82.
16. Agency for Healthcare Research and Quality. HCUP NIS Database Documentation: Healthcare Cost and Utilization Project. HCUP, 2018. Available at: www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed July 2, 2019.
17. Hosmer DW, Lemesbow S. Goodness of fit tests for the multiple logistic regression model. Commun Stat-Theor M 1980;9:1043-69.
18. Kramer DB, Tsai T, Natarajan P, et al. Frailty, physical activity, and mobility in patients with cardiac implantable electrical devices. J Am Heart Assoc 2017;6:e004659.
19. Ayaz T, Sahin SB, Sahin OZ, Bilir O, Rakıcı H. Factors affecting mortality in elderly patients hospitalized for nonmalignant reasons. J Aging Res 2014;2014:584315.
20. Zhan C, Baine WB, Sedrakyan A, Steiner C. Cardiac device implantation in the United States from 1997 through 2004: a population-based analysis. J Gen Intern Med 2008;23(suppl 1):13-9.
21. Romeyer-Bouchard C, Da Costa A, Dauphinot V, et al. Prevalence and risk factors related to infections of cardiac resynchronization therapy devices. Eur Heart J 2010;31:203-10.
22. Nery PB, Fernandes R, Nair GM, et al. Device-related infection among patients with pacemakers and implantable defibrillators: incidence, risk factors, and consequences. J Cardiovasc Electrophysiol 2010;21:786-90.
23. Gitenay E, Molin F, Blais S, et al. Cardiac implantable electronic device infection: detailed analysis of cost implications. Can J Cardiol 2018;34:1026-32.
24. Harcombe AA, Newell SA, Ludman PF, et al. Late complications following permanent pacemaker implantation or elective unit replacement. Heart 1998;80:240-4.
25. Arora RC, Brown CH, Sanjanwala RM, McKelvie R. "NEW" prehabilitation: a 3-way approach to improve postoperative survival and health-related quality of life in cardiac surgery patients. Can J Cardiol 2018;34:839-49.
26. Birman-Deych E, Waterman AD, Yan Y, et al. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. Med Care 2005;43.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.07.632.