International Journal of Cardiology 370 (2023) 204–208

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Determinants and prognostic value of in-hospital infection in patients waiting for permanent pacemaker implantation

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ARTICLE INFO

Keywords:
Pacemaker
Nosocomial infection
Temporary pacing
Hospitalization

ABSTRACT

Background: In-hospital delays in permanent cardiac pacemaker (PPM) implantation are common and may result in in-hospital infection among patients waiting for PPM implantation (pre-PPM-HI). This study investigated the predictors and prognostic impact of these events.

Methods: We retrospectively evaluated 905 consecutive patients (68.2 ± 16.0 years; 54% males) who underwent PPM implantation. Clinical characteristics, pre-PPM-HI and 30-day mortality were recorded and a risk score for pre-PPM-HI was generated using multivariable logistic regression coefficients.

Results: Eigthy-nine patients (10% of the sample) developed pre-PPM-HI. Multivariable logistic regression analysis identified urinary catheter use, complete atrioventricular block, implantation of temporary pacemaker and diabetes mellitus as independent predictors of pre-PPM-HI. The generated score (range 0–10.1) played a better role in predicting pre-PPM-HI than individual factors, yielding an area under the curve [95%CI] of 0.754 [0.705–0.803]. Patients with score ≥ 7.5 had 18-fold greater risk of developing pre-PPM-HI than those with score < 2.5. Furthermore, multivariable Cox-regression analysis showed that patients who developed pre-PPM-HI had greater 30-day mortality after PPM implantation (hazard ratio [95%CI] = 2.90 [1.18–7.16], $p = 0.021$) compared with their counterparts.

Conclusions: This study reveals that pre-PPM-HI is an independent predictor of early mortality after PPM implantation. In addition, a clinical score developed from simple clinical variables accurately identified patients at high risk of pre-PPM-HI. In scenarios where delays in PPM implantation are unavoidable, such as reference hospitals with high demand, the use of this tool can potentially help in the hierarchy of patients and in the reduction of this adverse event.

1. Introduction

Cardiac stimulation is commonly used to treat symptomatic high-grade atrioventricular (AV) block or bradycardia [1,2]. It is estimated that approximately 1.25 million permanent pacemakers (PPM) are implanted every year worldwide [3]. The high demand for PPM implantation is especially evident in tertiary or reference hospitals where clinical cases with indication for this procedure are concentrated. In this

Abbreviations: AUC, under the curve; AV, atrioventricular; PPM, permanent pacemakers; pre-PPM-HI, in-hospital infection during the waiting period prior to PPM implantation.

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https://doi.org/10.1016/j.ijcard.2022.10.140
Received 20 April 2022; Received in revised form 8 September 2022; Accepted 19 October 2022
Available online 23 October 2022

scenario, PPM is often delayed because of logistic issues, including lack of available operating rooms or catheterization laboratories and PPM devices [4,5].

Delays in PPM are naturally associated with prolonged use of temporary transvenous pacemaker, extended bed rest, and increased length of hospital stay [4–7]. As it might be expected, this latency may lead to a substantial increase in complications, including the development of in-hospital infection during the waiting period prior to PPM implantation (pre-PPM-HI) [4,5]. Although much attention has been devoted to the determinants and prognosis of infection of PPM after its implantation [8–12], there is still a lack of an effective tool for predicting the risk of pre-PPM-HI, which could eventually help in the ranking of priority patients for PPM implantation. This study evaluated the prevalence, predictors and prognostic value of pre-PPM-HI among patients who hospitalized and underwent PPM implantation. In addition, we developed a risk score constructed from clinical variables to predict the development of pre-PPM-HI.

2. Methods

2.1. Study population

This study retrospectively evaluated 905 consecutive patients who were admitted to a tertiary hospital (Clinics Hospital of the University of Campinas) and implanted PPM from 1986 to 2020. This hospital is a regional reference center located in the Southeast region of Brazil where patients are referred for PPM implantation. The study protocol was approved by The Ethics committee of the University of Campinas, which waived the requirement for informed consent. The authors had full access to all the data in the study and take responsibility for its integrity and the data analysis.

2.2. Clinical variables

Information regarding clinical and laboratory variables at the time of PPM implantation was thoroughly obtained from medical charts and comprised the following data: sex, age, body mass index, systolic and diastolic blood pressure and heart rate at admission, history of hypertension, diabetes mellitus, ever smoking, coronary heart disease, heart failure, previous stroke, Chagas disease, use of medications that might cause bradycardia (beta-blockers, calcium channel blockers, digoxin, amiodarone, central alpha2-agonists and ivabradine) and serum levels of potassium and creatinine. Data regarding use of urinary catheter or temporary transvenous pacemaker before PPM implantation among patients who did not have pre-PPM-HI and before pre-PPM-HI among patients who had pre-PPM-HI were also gathered. Patients with self-reported diagnosis of hypertension or use of antihypertensive medications were defined as having hypertension, while those with self-reported diagnosis of diabetes mellitus or use of anti-diabetic medications were defined as having diabetes. Coronary heart disease was defined as a history of former myocardial infarction or acute coronary syndrome or documentation of cardiac ischemia by coronary angiography or noninvasive tests (myocardial perfusion scintigraphy, stress echocardiography or exercise test). Heart failure was considered when this diagnosis was consistently reported in medical charts. Chagas Disease was considered when there were positive serologic tests for *T. cruzi* or this diagnosis was consistently reported in medical charts. Information on pacemaker characteristics was also gathered from the charts and included data on: pacemaker indication (due to sinus node disease, atrial fibrillation with low ventricular response, second degree AV block or complete AV block), and whether pacemaker implantation had urgent (defined as the presence of symptomatic AV conduction disturbance or sinus dysfunction requiring hospital admission within seven days of the diagnosis) [13] or elective indication. The diagnosis of pre-PPM-HI was defined as any infection which symptom started after 48 h of hospitalization, was followed by antibiotic treatment and occurred before PPM implantation [14]. Patients who developed infections within the first 48 h of hospitalization were included in the analysis, but were considered as part of the patients who did not develop pre-PPM-HI.

2.3. Outcomes

The main outcome was all-cause death up to 30 days post-PPM implantation. The clinical status up to the 30th day was assessed by medical recordings or by vital status according to the national social security number database for those patients who had hospital discharge. The causes of death were ascertained by medical chart review or death certificates. Additional outcomes included: in-hospital mortality post-PPM implantation, the period between hospital admission and implantation of PPM, and total in-hospital length of stay.

2.4. Statistical analysis

Categorical variables and continuous variables with normal and non-normal distribution are presented as numbers (proportions), mean ± standard deviation and median [25th, 75th percentiles]. Differences in studied variables were evaluated by $\chi 2$ test for categorical variables, unpaired *t*-test for normally distributed variables, and Mann-Whitney test for non-normally distributed variables. Multivariable forward stepwise logistic regression analysis including age, sex, calendar time and the variables that showed significant relationship with pre-PPM-HI in univariate analysis were used to determine the final model of the regression and to build an equation that generated a score to predict pre-PPM-HI. Univariate logistic regression analysis was performed to evaluate the association of pre-PPM-HI with the generated score. The area under the curve (AUC) resulting from receiver operator characteristics analysis estimated the accuracy of clinical variables and the generated score to predict pre-PPM-HI. The Stata *roccomp* command was used to compare the AUCs (https://www.stata.com/manuals/rroccomp.pdf). The calibration of the score model was assessed by the Hosmer-Lemeshow test. Cumulative death rate up to 30 days after PPM implantation was calculated by the Kaplan–Meier method, and the curves were compared by log-rank test. Multivariable forward stepwise Cox-regression analysis including all studied characteristics, calendar time and pre-PPM-HI was used to identify the independent predictors of 30-day mortality after PPM implantation. Statistical analysis was performed using Stata software V.14.2 (Stata Corp LP, College Station, Texas, USA). *P*-values <0.05 were considered statistically significant.

3. Results

3.1. Prevalence and determinants of pre-PPM-HI

The studied sample comprised 905 participants (68.2 ± 16.0 years; 54% males; 91% with urgent PPM implantation) who were admitted to the hospital and implanted PPM. Of these, 89 (10%) developed pre-PPM-HI. Most pre-PPM-HI events were due to urinary tract infection (34%) and pneumonia (34%), but alternative etiologies, including bloodstream (18%), catheter-related (7%), and skin (4%) infections, as well as sepsis of unknown origin or endocarditis (3%) also occurred. Conversely, only one patient developed in-hospital infection (aspiration pneumonia) within 48 h since hospital admission.

The characteristics of the sample according to those who developed or not pre-PPM-HI are shown in Table 1. Patients who had pre-PPM-HI had greater prevalence of hypertension, diabetes, heart failure and were more likely to have complete AV block and to have used urinary catheter and implanted a temporary transvenous pacemaker than those who did not have pre-PPM-HI. The median time [25th, 75th percentiles] between hospital admission and the diagnosis of pre-PPM-HI was 6 [3, 8] days.

Multivariable stepwise logistic regression analysis including age, sex and the variables that showed significant relationship with pre-PPM-HI in univariate analysis demonstrated that urinary catheter use [odds ratio

Table 1
Characteristics of the participants.

Variables	No pre-PPM-HI ($n = 816$)	pre-PPM-HI ($n = 89$)	p-value
Baseline clinical characteristics			
Age, years	68.0 ± 15.8	70.4 ± 17.1	0.18
Female sex, %	45	55	0.07
Body mass index, kg/m^2	25.6 ± 5.4	25.5 ± 5.6	0.95
Systolic blood pressure, mmHg	141 ± 35	138 ± 34	0.37
Diastolic blood pressure, mmHg	79 ± 17	76 ± 17	0.13
Heart rate, bpm	51 ± 20	49 ± 20	0.39
Hypertension, %	64	78	0.009
Diabetes mellitus, %	23	39	<0.001
Heart failure, %	24	36	0.010
Ever smoking, %	32	40	0.12
Coronary artery disease, %	14	19	0.16
Previous stroke, %	9	12	0.29
Chagas Disease, %	22	18	0.43
Urinary catheter use*, %	14	47	<0.001
Beta-blockers, %	15	17	0.73
Calcium channel blockers	11	17	0.10
Digoxin	6.7	6.7	1.00
Amiodarone	6.5	4.5	0.46
Central alpha2-agonists	3.3	3.4	0.98
Ivabradine	0.1	0	0.74
Biochemical profile			
Potassium, mEq/L	4.3 ± 0.7	4.3 ± 0.7	0.82
Creatinine, mg/dL	1.08 [0.87, 1.37]	1.06 [0.80, 1.38]	0.45
Pacemaker characteristics			
Urgent / Elective, %	90 / 10	94 / 6	0.21
Pacemaker indication, %			0.020
Sinus Node Disease	8	2	
AF with low ventricular response	4	3	
Second degree AV block	18	10	
Complete AV block	69	84	
Temporary pacemaker*, %	58	82	<0.001

AF – atrial fibrillation; AV – atrioventricular; PPM – permanent pacemaker; pre-PPM-HI – in-hospital infection during the waiting period prior to PPM implantation with symptoms starting after 48 h of hospitalization.
* Before PPM implantation among patients who did not have pre-PPM-HI and before pre-PPM-HI among patients who had pre-PPM-HI.

(95% CI) = 4.51 (2.78–7.32); $p < 0.001$], complete AV block [odds ratio (95% CI) = 1.95 (1.05–3.63); $p = 0.035$], implantation of temporary pacemaker [odds ratio (95% CI) = 1.88 (1.04–3.42); $p = 0.037$] and diabetes mellitus [odds ratio (95% CI) = 1.66 (1.03–2.68); $p = 0.038$] were independently associated with pre-PPM-HI, while hypertension, heart failure, age and sex were not (Supplemental Fig. 1). Furthermore, pre-PPM-HI patients who used urinary catheter had similar type of infections than those who did not used urinary catheter (Supplemental Table 1).

Based on the regression coefficients derived from the multivariable model, we built the following equation to generate a score for predicting the development of pre-PPM-HI:

Score = [urinary catheter use (Yes = 1/No = 0) * 4.5] + [complete AV block (Yes = 1/No = 0) * 2.0] + [Temporary pacemaker (Yes = 1/No = 0) * 1.9] + [diabetes (Yes = 1/No = 0) * 1.7].

The generated score yielded median [25th, 75th percentiles] values of 3.9 [1.9, 5.5] (range = 0 to 10.1) and showed a direct association with pre-PPM-HI (Supplemental Fig. 2). We then divided the sample into four groups based on arbitrary score cutoffs (<2.5; ≥2.5 and < 5.0; ≥5.0 and < 7.5; ≥7.5) and found that the group with greatest score (≥7.5) had a 18-fold greater risk of developing pre-PPM-HI than the group with lowest score (<2.5) (Table 2). Individual risk factors had limited discriminatory ability to predict pre-PPM-HI, yielding AUC values ranging from 0.576 to 0.668, while the generated score presented as continuous variable or split into arbitrary groups had the greatest accuracy (AUC = 0.754 and 0.750, respectively; $p < 0.001$ compared with individual risk factors) (Table 3). Furthermore, the Hosmer-Lemeshow test resulted in a p value of 0.17, indicating good score model calibration.

Table 2
Incidence and relative risk of pre-PPM-HI according to score arbitrary groups.

Score	N	pre-PPM-HI cases	Incidence of pre-PPM-HI (%)	Odds Ratio (95% CI)	p-value
<2.5	345	8	2.3	Ref	
≥2.5 and < 5.0	323	27	8.4	3.84 (1.72–8.59)	<0.001
≥5.0 and < 7.5	118	19	16.1	8.08 (3.43–19.03)	<0.001
≥7.5	119	35	29.4	17.55 (7.85–39.2)	<0.001

CI – confidence interval; pre-PPM-HI – in-hospital infection during the waiting period prior to PPM implantation with symptoms starting after 48 h of hospitalization.

3.2. Outcomes

Regarding the whole sample, the median [25th, 75th percentiles] and mean ± standard deviation in-hospital waiting period for PPM implantation and total in-hospital length of stay were 5 [2, 9] and 7.5 ± 8.9 days, and 7 [3,12] and 9.9 ± 12.0 days, respectively. Conversely, the patients who developed pre-PPM-HI had greater in-hospital waiting period for PPM implantation (median [25th, 75th percentiles] = 17 [13, 24] vs. 4 [2, 8] days; $p < 0.001$) and greater total in-hospital length of stay (median [25th, 75th percentiles] = 21 [14, 31] vs. 6 [3,10] days; p < 0.001) than those who did not develop pre-PPM-HI.

Chi-squared analysis showed that patients who developed pre-PPM-HI had greater in-hospital mortality after PPM implantation compared with those who did not develop pre-PPM-HI (5.6% vs. 1.6%, $p = 0.010$). During a median [25th, 75th percentiles] follow-up of 30 [30,30] days after PPM implantation, there were 7 (7.9%) and 17 (2.1%) deaths among participants who developed and did not develop pre-PPM-HI, respectively. Kaplan–Meier analysis showed that pre-PPM-HI was associated with greater mortality (Log-rank test, $p = 0.001$) (Fig. 1), while multivariable forward stepwise Cox-regression analysis including all studied characteristics, calendar time and pre-PPM-HI as independent variables showed that 30-day mortality was associated with heart failure (hazard ratio [95%CI] = 4.35 [1.87–10.12], p = 0.001), age (hazard ratio [95%CI] = 1.06 [1.02–1.11], $p = 0.003$) and pre-PPM-HI (hazard ratio [95%CI] = 2.90 [1.18–7.16], $p = 0.021$). The causes of 30-day death in patients who developed or not pre-PPM-HI were statistically similar, and were mostly related to sudden death/cardiogenic shock and sepsis (Supplemental Table 2).

4. Discussion

The present study evaluating the predictors and prognostic value of

Table 3
Accuracy of studied variables to predict pre-PPM-HI.

Variables	Area under the curve [95% CI]
Complete atrioventricular block	0.576 [0.535, 0.618]*
Diabetes mellitus	0.581 [0.528, 0.634]*
Temporary pacemaker	0.622 [0.579, 0.666]*
Urinary catheter use	0.668 [0.614, 0.721]*
Score (Arbitrary groups)	0.750 [0.701, 0.800]
Score (Continuous variable)	0.754 [0.705, 0.803]

CI – confidence interval.
pre-PPM-HI – in-hospital infection during the waiting period prior to PPM implantation with symptoms starting after 48 h of hospitalization.
* $P < 0.05$ compared with score (split into arbitrary groups or as a continuous variable).

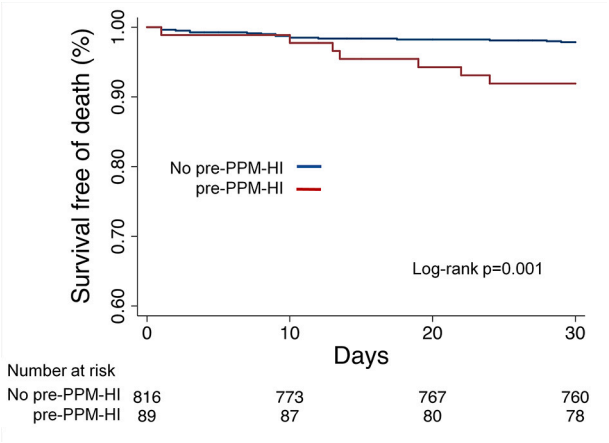

Fig. 1. Kaplan Meier curves for 30-day mortality after permanent pacemaker implantation. pre-PPM-HI – in-hospital infection during the waiting period prior to PPM implantation with symptoms starting after 48 h of hospitalization.

pre-PPM-HI generated three major results. First, use of urinary catheter, complete AV block, temporary pacing and diabetes mellitus were independently associated with pre-PPM-HI incidence. Second, a combined risk score built from these variables had a fair ability to predict the development of pre-PPM-HI. Third, pre-PPM-HI was independently associated with greater 30-day mortality after PPM implantation. These data indicate that pre-PPM-HI is a predictor of early mortality following PPM implantation. Furthermore, the novel score proposed herein could be a potential tool to identify patients at higher risk of developing pre-PPM-HI.

One major aim of our investigation was to identify predictors of pre-PPM-HI. It is noteworthy that this outcome differs from that usually assessed in most available studies, which have focused on the infection of cardiac implantable electronic devices, including PPM, after their implantation [10–12]. Consistent with the findings in PPM implant site infections [10–12], diabetes mellitus and temporary pacing were found to be independent predictors of pre-PPM-HI, suggesting a common pathophysiological background. In contrast with implant site infections, complete AV block and use of urinary catheter were also identified as predictors of pre-PPM-HI. Notably, use of urinary catheter emerged as the strongest predictor of pre-PPM-HI and was associated with all types of pre-PPM-HI and not only with urinary tract infection, suggesting that this variable might capture and cluster clinical conditions that would be associated with higher susceptibility to develop pre-PPM-HI. Finally, we observed that the use of a risk score based on this set of predictors has a good accuracy in identifying the risk of pre-PMM-HI. In clinical scenarios where delays in PPM implantation are unavoidable, such as reference hospitals with high demand, the use of this score can potentially help in the ranking of priority patients for PPM implantation and in the reduction of this adverse event.

Although pre-PPM-HI is assumed to increase the morbidity of affected patients [4], it is not established whether it may also influence mortality among patients who implanted PPM. In our analysis, pre-PPM-HI was related to greater in-hospital mortality and was independently associated with higher mortality after 30 days of PPM implantation. The reasons for the greater mortality among patients who had pre-PPM-HI is not clear in our analysis, since the causes of death between patients who developed or not pre-PPM-HI tended to be similar. Importantly, the rate of death due to sepsis was similar between patients who developed or not pre-PPM-HI, suggesting that pre-PPM-HI might have been adequately treated prior to PPM implantation. Conversely, it can be argued that the greater rate of comorbidities among patients who developed pre-PPM-HI and the excessive expenditure of functional reserve to overcome the in-hospital infection prior to PPM implantation might have contributed to the greater mortality in these patients. Regardless of the underlying mechanisms, our data indicate that pre-PPM-HI may be used as marker of adverse prognosis among patients who implanted PPM, although further studies are necessary to evaluate whether implementing strategies focused on abrogating the development of pre-PPM-HI would reduce the early mortality rate after PPM implantation.

Additional results of this report deserve further comments. First, 10% of our sample developed pre-PPM-HI, which was mostly accounted for urinary tract infection and pneumonia. These findings are very similar to those reported by a previous retrospective Danish study, which reported that 11% of patients referred for PPM implantation developed pre-PPM-HI, mostly due to urinary tract infection and pneumonia [4], and strengthen the notion that the incidence of pre-PPM-HI might be substantial in the real world. Second, the median time between hospital admission and PPM implantation is reported to be around 8 days in several centers worldwide [4,5,15], which is similar to that observed in our studied population. Third, our patients who developed pre-PPM-HI implanted PPM after a median of 13 days compared with those who did not develop pre-PPM-HI. Likewise, Irfan et al. showed that pre-PPM-HI delayed the implantation of PPM in average by 7.2 days [5], confirming that pre-PPM-HI is associated with greater in-hospital length of stay, which may generate higher hospital costs and limit the availability of hospital beds to alternative patients [16,17].

This report has some limitations. First, this was and observational and retrospective study. Therefore, unmeasured confounding factors may have influenced the observed associations. Second, our study population only included patients who effectively implanted PPM, while those who required PPM implantation but died before the procedure were not included in the analysis. Thus, the present findings cannot be generalized to all hospitalized patients with indication for PPM implantation.

In conclusion, the current analysis demonstrated that pre-PPM-HI is an independent predictor of early mortality following PPM implantation. Furthermore, the present report disclosed several risk factors associated with the development of pre-PPM-HI and provided a novel risk score based on these factors. This novel score might be useful to identify in-hospital patients at higher risk of developing pre-PPM-HI that could be targets for earlier PPM implantation, closer clinical surveillance and more aggressive prophylaxis of in-hospital infections.

Funding

The study was supported by a grant from the Brazilian National Council for Scientific and Technological Development (CNPq; grant 310869/2021–8) and São Paulo Research Foundation (FAPESP 2013/07607–8) for Dr. Nadruz.

Role of the funding source

None.

Author statement

MCB, WC and WNJ contributed to the design of the work, to the acquisition, analysis and interpretation of data and drafted the work. FP, MJOF, OMS, MMF-S, RS, MFRAO, PPMO, LMS-F, OPJ, ORCF-H, JRM-S, ACS contributed to the acquisition, analysis and/or interpretation of data and revised the manuscript critically for important intellectual content. All authors approved the version published and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Competing Interest

None.

Acknowledgements

None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.10.140.

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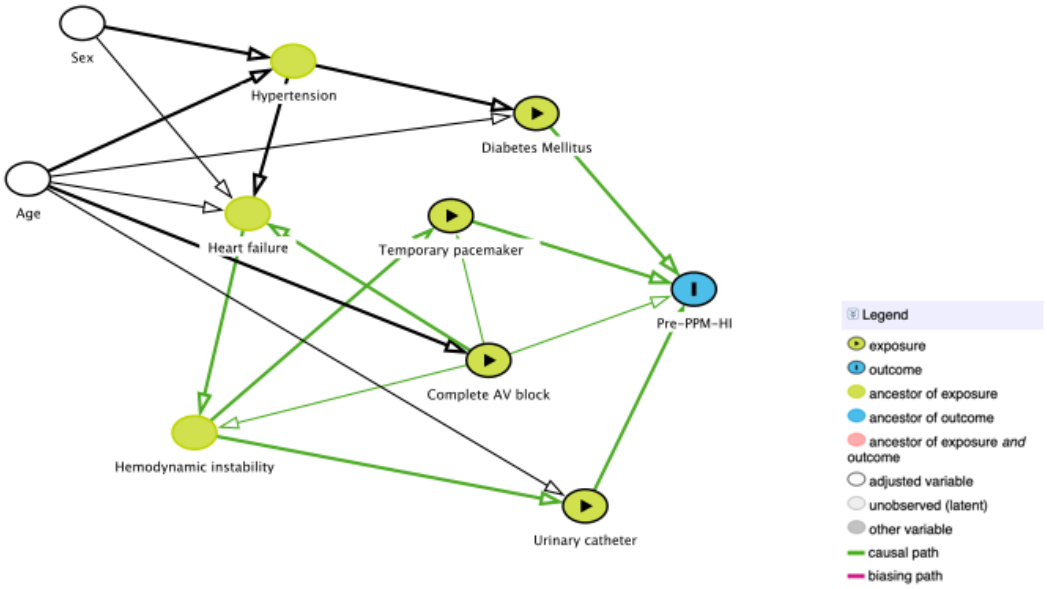
SUPPLEMENTAL MATERIAL

Supplemental Figure 1. **Directed Acyclic Graph (DAG) showing the predictors of pre-PPM-HI**



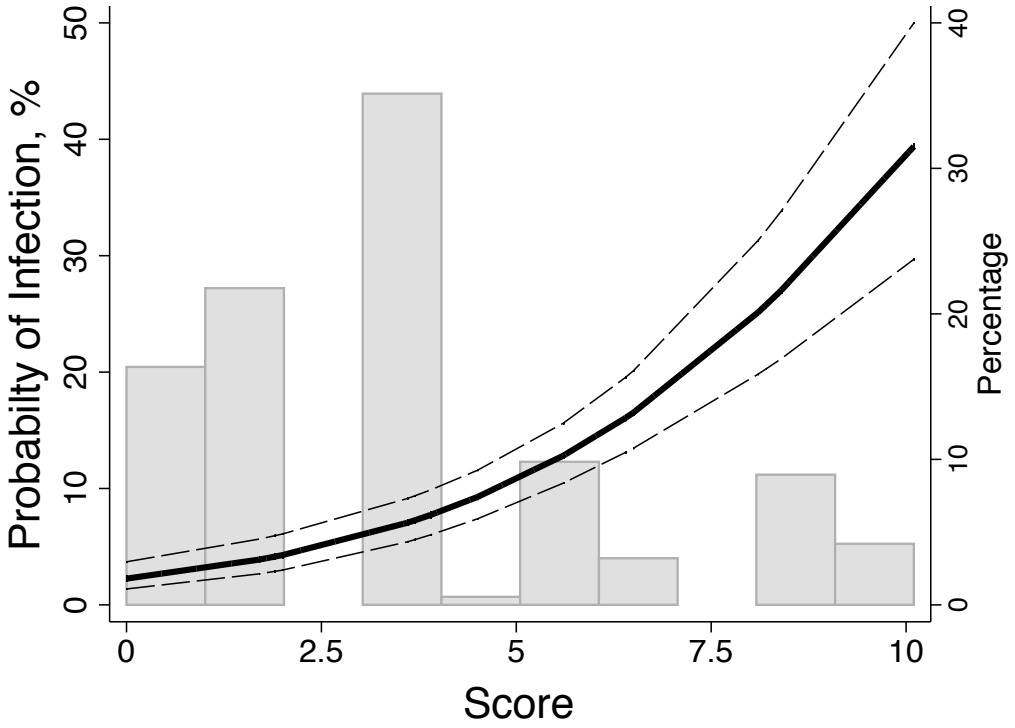
AV – atrioventricular; pre-PPM-HI – in-hospital infection during the waiting period prior to PPM implantation with symptoms starting after 48 hours of hospitalization.

Supplemental Table 1. Types of pre-PPM-HI among patients who used or not urinary catheter

	Not used urinary catheter (n-47)	Used urinary catheter (n=42)	p-value
Types of pre-PPM-HI			0.51
Urinary tract infection	14 (30)	16 (38)	
Penumonia	14 (30)	16 (38)	
Bloodstream infection	11 (23)	5 (12)	
Skin infection	3 (6)	1 (2)	
Catheter-related infection	4 (9)	2 (5)	
Sepsis of unknown origin/Endocarditis	1 (2)	2 (5)	

pre-PPM-HI – in-hospital infection during the waiting period prior to PPM implantation with symptoms starting after 48 hours of hospitalization.

Supplemental Figure 2. Logistic regression analysis between the generated score and pre-PPM-HI.



The dashed lines indicate the 95% confidence intervals. The gray bars are histograms of the distribution (in percentage) of the score.
pre-PPM-HI – in-hospital infection during the waiting period prior to PPM implantation with symptoms starting after 48 hours of hospitalization.

Supplemental Table 2. Causes of death among patients who died up to 30 days after permanent pacemaker implantation

	No pre-PPM-HI n=17	pre-PPM-HI n=7	p-value
Causes of death, n (%)			0.51
Sudden death/cardiogenic shock	8 (47)	3 (43)	
Sepsis	8 (47)	3 (43)	
Cancer	1 (6)	0 (0)	
Duoden perforation	0 (0)	1 (14)	

pre-PPM-HI – in-hospital infection during the waiting period prior to PPM implantation with symptoms starting after 48 hours of hospitalization.