Evaluation of Death among the Patients Undergoing Permanent Pacemaker Implantation: A Competing Risks Analysis

Haleh GHAEM¹, *Mohammad GHORBANI², Samira ZARE DORNIANI³

¹. Research Center for Health Sciences, Institute of Health, Dept. of Epidemiology, School of Health, Shiraz University of Medical Sciences, Shiraz, Iran
². Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran
³. Anesthesiology and Critical Care Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

*Corresponding Author: Email: ghorbani_epi@yahoo.com
(Received 04 Jul 2016; accepted 20 Dec 2016)

Abstract
Background: Permanent artificial pacemaker is one of the important therapies for treatment of cardiac conduction system problems. The present study aimed to determine the association between some predictive variables and all-cause and cause-specific mortality in the patients who had undergone pacemaker implantation.

Methods: This study was conducted on 1207 patients who had undergone permanent pacemaker implantation in the hospitals affiliated with Shiraz University of Medical Sciences, Iran, from Mar 2002 to Mar 2012. The variables that existed in the patients’ medical records included sex, diabetes mellitus, obesity, cerebrovascular accident, cardiomegaly, smoking, hypertension, ischemic heart disease, congenital heart disease, sick sinus syndrome, and atrial fibrillation. Competing risks model was used to assess the association between the predictive variables and cause-specific (i.e., cardiac and vascular) mortality.

Results: The patients’ mean age was 66.32±17.92 yr (70.62±14.45 yr in the patients with single-chamber pacemakers vs. 61.91±17.69 yr in those with two-chamber pacemakers) (P<0.001). Sick sinus syndrome and age increased the risk of all-cause mortality, while two-chamber pacemaker decreased this risk. Obesity increased the risk of cardiac death, and diabetes mellitus and heart valve disease increased the risk of vascular death.

Conclusion: The variables predicting mortality in all-cause model were completely different from those in cause-specific model. Moreover, death in such patients may occur due to reasons other than pacemaker. Therefore, future studies, particularly prospective ones, are recommended to use competing risks models.

Keywords: Pacemaker, Competing for risk, Sick sinus syndrome

Introduction

Using permanent artificial pacemaker is one of the important therapies for treatment of cardiac conduction system problems (1). The first artificial pacemaker was implanted about 60 yr ago and more than 400 thousand pacemakers are implanted for patients around the world each year. Today, with advancement of technology, very advanced pacemakers are available (2). Progress in pacemaker technology in the past decade indicates the necessity to update pre-implantation determinants of patient’s prognosis (3).

Long-term survival after implantation is one of the important issues in evaluation and selection of a permanent artificial pacemaker. For time to event data, Kaplan-Meier survival analysis methods are usually employed. However, patients with permanent artificial pacemakers may die for reasons other than the pacemaker. Therefore, there is a competing risks situation where Kaplan-Meier survival analysis is not appropriate. Most of the studies assessed the association between pacemaker mode and cause-specific mor-
tality, have failed to consider the “competing risks” of other causes of death (4-8). When there are no or low competing risks, Cox regression model is suitable to be used. However, in case of high competing risks, especially in the elderly patients (9), this method may overestimate the absolute risk of the event of interest. Cox method assumes that the cases that die and censored because of competing risks can experience the event of interest in future, which is wrong (10). Moreover, when there is a competing risks situation, survival methods cannot accurately predict the probability of survival rate (11-15). Thus, using competing risks is suitable in diseases, such as heart disease and cancers where there are multiple failure types, because it can estimate the impact of exposure to different causes of death accurately (16). No studies have been conducted on the relationship between pacemaker mode and its changes and cause-specific mortality using competing risks models. Therefore, the present study aimed to determine the association between pacemaker mode and all-cause and cause-specific mortality in the patients who had undergone pacemaker implantation in the hospitals affiliated with Shiraz University of Medical Sciences, Iran, from Mar 2002 to Mar 2012.

Methods

This study was conducted on 1207 patients who had undergone permanent pacemaker implantation. The data were collected from the patients’ medical records. The variables that existed in the medical records included sex, diabetes mellitus, cerebrovascular accident, obesity, smoking, cardiomegaly, hypertension, congenital heart disease, ischemic heart disease, sick sinus syndrome and atrial fibrillation. The patients’ survival was determined by phone contact. Additionally, the leading cause of the patients’ death was extracted from the registration system of the Department of Health of Shiraz University of Medical Sciences, Iran. Competing risks situation arises when an individual experiences more than one type of event and occurrence of an event (death from vascular disease) prevents the occurrence of another event (death from cardiac disease) (17, 18). When there are competing risks situations, Kaplan-Meier estimation cannot be interpreted as a probability; therefore, a specific approach is required based on the cumulative incidence function (19). Competing risks regression models allow us to identify independent risk factors for two events (death from cardiac and vascular diseases) and to create two different algorithms. In survival analysis, in many data sets, there is one favorite event and for each person, there is only one failure time and one cause of failure (type of event) (20). In some circumstances, it is possible that every subject experiences the event because of one of k causes (k>2), called competing risks (21). For example, if we are interested in the analysis of time to death because of heart disease, factors other than heart disease that result in death are called competing risks. Hence, in competing risks data, there are at least two causes for failure that compete with each other for happening. When an individual experiences an event other than the desired event, the probability of the desired event will change. Therefore, it is necessary to perform competing risks analysis (22). Analysis of survival data of competing risks has recently shown advantages over standard survival analyses. Regression competing risks modeling allows identification of independent risk factors (23).

Statistical Analysis

In this study, continuous variables were presented as mean ± Standard Deviation. Cox proportional hazards regression was used to examine the relationship between the potential risk factors and all-cause mortality. In addition, competing risks model (24) was used to evaluate the association between the predictive variables and cause-specific (i.e., cardiac and vascular) mortality. In this study, time-to-death (month) was the primary outcome variable and P<0.05 was considered
statistically significant. Data analyses were performed using Stata software package, ver. 13.

**Results**

The patients’ mean ± SD age was 66.32±17.92 yr (65.01±19.98 yr in males vs. 67.42±15.78 yr in females) \( (P<0.001) \). According to Table 1, among the study patients, 52.3% were female and 47.6% were male. Baseline characteristics of the participants have been presented in Table 1.

Until Mar 2012, 252 deaths (20.88%) were reported out of which, 46 (18.25%) were cardiac and 16 (6.35%) were vascular. In addition, 190 deaths (75.40%) were due to other causes. Totally, 955 cases were censored. The patients’ mean and median survival times were 50.58±35.61 and 51 months, respectively. Besides, the mean survival times of the patients with single-chamber and two-chamber pacemakers were 54.40±34.62 and 49.69±34.95 months, respectively.

| Variables                          | Frequency | Percent | \( P \)-value |
|------------------------------------|-----------|---------|---------------|
| Sex                                | Male      | 429     | 47.6          | 0.149         |
|                                    | Female    | 472     | 52.3          |               |
| Diabetes mellitus                  | Yes       | 107     | 11.86         | 0.001         |
|                                    | No        | 795     | 88.14         |               |
| Obesity                            | Yes       | 1       | 0.02          | 0.001         |
|                                    | No        | 901     | 99.98         |               |
| Cerebrovascular accident           | Yes       | 39      | 4.32          | 0.001         |
|                                    | No        | 863     | 95.68         |               |
| Cardiomegaly                       | Yes       | 4       | 0.04          | 0.001         |
|                                    | No        | 898     | 99.96         |               |
| Smoking                            | Yes       | 128     | 14.19         | 0.001         |
|                                    | No        | 774     | 85.81         |               |
| Hypertension                       | Yes       | 353     | 39.13         | 0.001         |
|                                    | No        | 549     | 60.87         |               |
| Ischemic heart disease             | Yes       | 283     | 31.37         | 0.001         |
|                                    | No        | 619     | 68.62         |               |
| Congenital heart disease           | Yes       | 9       | 1.00          | 0.001         |
|                                    | No        | 893     | 99.00         |               |
| Valvular heart disease             | Yes       | 194     | 21.51         | 0.001         |
|                                    | No        | 708     | 78.49         |               |
| Cardiomyopathy                     | Yes       | 10      | 1.11          | 0.001         |
|                                    | No        | 892     | 98.89         |               |
| Syncope                            | Yes       | 105     | 11.64         | 0.001         |
|                                    | No        | 797     | 88.36         |               |
| Atrioventricular block             | Yes       | 566     | 62.75         | 0.001         |
|                                    | No        | 336     | 37.25         |               |
| Sick sinus syndrome                | Yes       | 92      | 10.20         | 0.001         |
|                                    | No        | 810     | 89.80         |               |
| Atrial fibrillation                | Yes       | 17      | 1.88          | 0.001         |
|                                    | No        | 885     | 98.12         |               |
**All-cause and cause-specific mortality**

According to Table 2, age (HR=1.01, 95% CI: 1.00-1.02) and sick sinus syndrome (HR=1.65, 95% CI: 1.11-2.46) increased the risk of all-cause mortality, while two-chamber pacemaker (HR=0.68, 95% CI: 0.49-0.95) decreased the risk of all-cause mortality.

The results also showed that obesity (HR=21.83, 95% CI: 2.87-166.10) increased the risk of cardiac death, while valvular heart disease (HR=2.90, 95% CI: 1.01-8.29) and diabetes mellitus (HR=7.15, 95% CI: 4.08-20.12) increased the risk of vascular death (Fig.1).

**Discussion**

Assessment of the relationship between exposure and favorite event in the presence of competing risks is one of the advanced aspects of survival analysis.

Moreover, the factors affecting the prognosis of death are very important in patients with artificial cardiac pacemaker implantation.

In this retrospective cohort study, the following results were obtained. Firstly, a significant relationship was found between age and all-cause mortality, such a way that older groups had a greater risk of death. This was consistent with the findings of the other studies (25, 26). As expected, age was an independent prognostic factor, with every year increasing the risk of death by 5% (1). A 9% (univariate) increase was reported in mortality in the subgroup of older patients (2). Yet, future studies with larger sample sizes are necessary to investigate the long-term survival after pacemaker implantation in different age groups, especially children.

### Table 2: The relationship between the study factors and all-cause / cause-specific mortality

| Variables                      | Cox regression All-cause death HR (95% CI) | Cox regression Cardiac death SHR (95% CI) | Cox regression Vascular death SHR (95% CI) |
|--------------------------------|------------------------------------------|----------------------------------------|------------------------------------------|
| Age                            | 1.01 (1.00-1.02)*                        | 1.03 (0.99-1.07)                       | 1.03 (0.97-1.08)                        |
| Sex                            | 0.95 (0.72-1.24)                         | 0.58 (0.30-1.15)                       | 0.47 (0.16-1.42)                       |
| Diabetes mellitus              | 1.15 (0.77-1.70)                         | 0.93 (0.33-2.64)                       | 7.15 (4.08-20.12)*                     |
| Blood sugar                    | 1.00 (1.00-1.00)                         | 1.00 (0.99-1.01)                       | 0.99 (0.95-1.03)                       |
| Obesity                        | 3.00 (0.42-21.42)                        | 21.83 (2.87-166.10)*                   | -                                       |
| Cerebrovascular accident       | 0.95 (0.45-2.02)                         | 1.71 (0.40-7.25)                       | 2.06 (0.27-15.77)                      |
| Cardiomegaly                   | 1.68 (0.24-12.03)                        | -                                      | -                                       |
| Creatinine                     | 1.11 (0.89-1.37)                         | 1.22 (0.89-1.67)                       | 1.00 (0.63-1.60)                       |
| Smoking                        | 0.92 (0.62-1.39)                         | 1.66 (0.72-3.81)                       | 1.06 (0.23-4.81)                       |
| Hypertension                   | 1.07 (0.81-1.41)                         | 1.28 (0.66-2.50)                       | 0.57 (0.18-1.82)                       |
| Systolic blood pressure        | 1.00 (0.99-1.00)                         | 0.99 (0.98-1.01)                       | 0.99 (0.96-1.02)                       |
| Diastolic blood pressure       | 0.99 (0.98-1.00)                         | 0.99 (0.97-1.03)                       | 0.99 (0.93-1.05)                       |
| Ischemic heart disease         | 1.01 (0.75-1.34)                         | 1.49 (0.75-2.93)                       | 0.83 (0.26-2.66)                       |
| Congenital heart disease       | 1.25 (0.31-5.02)                         | 3.57 (0.48-26.39)                      | -                                       |
| Valvular heart disease         | 1.10 (0.79-1.52)                         | 1.83 (0.89-3.77)                       | 2.90 (1.01-8.29)*                      |
| Cardiomyopathy                 | 0.91 (0.23-3.68)                         | -                                      | -                                       |
| Syncope                        | 0.78 (0.50-1.22)                         | 0.94 (0.33-2.71)                       | 1.20 (0.27-5.45)                       |
| Atrioventricular block         | 1.09 (0.82-1.44)                         | 0.83 (0.42-1.63)                       | 0.66 (0.23-1.86)                       |
| Sick sinus syndrome            | 1.65 (1.11-2.46)*                        | 0.96 (0.29-3.13)                       | 1.67 (0.37-7.59)                       |
| Atrial fibrillation            | 0.91 (0.34-2.46)                         | 1.38 (0.18-10.33)                      | -                                       |
| Pacemaker                      | 0.68 (0.49-0.95)*                        | 0.51 (0.22-1.21)                       | 0.38 (0.08-1.78)                       |

*P<0.05, 1 cardiac death, 2 vascular death, 3 other deaths

Available at:  [http://ijph.tums.ac.ir](http://ijph.tums.ac.ir)
Secondly, the present study results showed a significant relationship between sick sinus syndrome and all-cause mortality. Besides, a significant relationship was found between sick sinus syndrome and all-cause death (2).

Thirdly, single-chamber pacemaker had an adverse effect on all-cause death. A retrospective study was conducted on short-term survival with a 2-year follow-up and revealed that after adjusting for other factors, single-chamber pacemaker had an adverse effect on all-cause death (27). Similar results were also obtained in another study (2). Interestingly, the results of the MOST study demonstrated that the incidence of heart failure was higher in patients with single-chamber pacemakers compared to those with two-chamber pacemakers (28). This might also account for the difference in survival time in our study.

Fourthly, the current study findings disclosed a significant association between obesity and increased risk of cardiac mortality. Obesity is a risk factor for diabetes, hypertension, and dyslipidemia, which are risk factors for heart disease (29). Valvular heart disease and diabetes mellitus were associated with increased risk of vascular death.

The present study also aimed to provide a risk model for predicting death after permanent pacemaker implantation. Several studies have investigated long-term survival after pacemaker implantation using Kaplan–Meier method (2, 4–7). However, Kaplan–Meier estimates cannot be assumed as probabilities when competing risks are present.

Overall, the results and conclusions should be investigated with caution. Retrospective study design can result in bias. In this research, all the information was gathered from the patients’ medical records. Although much work was done on these data to change them into the standard format, most of the information was qualitative. In addition, there were a limited number of obese subjects, resulting in low statistical power. Thus, the findings related to the obese individuals
should be interpreted with caution. When statistical analysis was done between sub-groups, a type II error may occur. Hence, our results might have been influenced by residual confoundings, such as varying types of single-chamber pacemakers, not measured in this study. Moreover, no data was available about the variables not recorded in the patients’ medical records. Finally, the cause of mortality was determined by the registration system of the Department of Health of Shiraz University of Medical Sciences and the death certificates might have been biased by the choices of the physicians who filled them out. On the other hand, the strengths of this study included its representative population, relatively large sample size, and long-term follow-up. In addition, a unique aspect of this study was the ability to differentiate between the causes of death.

Conclusion

The variables predicting mortality in the all-cause model were completely different from those in the cause-specific model. Moreover, studies performed on pacemaker up to now have used survival analysis, while death in such patients may occur due to reasons other than pacemaker. Therefore, future studies, particularly prospective ones, are recommended to use competing risk models.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

The present paper was financially supported by Shiraz University of Medical Sciences (grant NO: 95-01-42-11539). Hereby, the authors would like to thank Ms. A. Keivanshekouh at the Research Improvement Center of Shiraz University of Medical Sciences for improving the use of English in the manuscript.

Conflict of Interests

The authors declare that there is no conflict of interest.

References

1. Ali-Akbari F, Khalifehzadeh A, Parvin N (2009). The effect of short time telephone follow-up on physical conditions and quality of life in patients after pacemaker implantation. Journal of Shahrakord University of Medical Sciences, 11:23-28.
2. Brunner M, Olschewski M, Geibel A, Bode C, Zehender M (2004). Long-term survival after pacemaker implantation - Prognostic importance of gender and baseline patient characteristics. Eur Heart J, 25:88-95.
3. Udo EO, van Hemel NM, Zuithoff NP, Doevendans PA, Moons KG (2013). Prognosis of the bradycardia pacemaker recipient assessed at first implantation: a nationwide cohort study. Heart, 99:1573-8.
4. Kim WH, Joung B, Shim J, Park JS, Hwang ES, Pak HN, Kim S, Lee M (2010). Long-term outcome of single-chamber atrial pacing compared with dual-chamber pacing in patients with sinus-node dysfunction and intact atrioventricular node conduction. Yonsei Med J, 51:832-7.
5. Marchandise S, Scavee C, le Polain de Waroux JB, de Meester C, Vanoverschelde JL, Debbas N (2012). Long-term follow-up of DDD and VDD pacing: a prospective non-randomized single-centre comparison of patients with symptomatic atrioventricular block. Europace, 14:496-501.
6. Ovsyshcher E, Hayes DL, Furman S (1998). Dual-Chamber Pacing Is Superior to Ventricular Pacing Fact or Controversy? Circulation, 97:2368-2370.
7. Vassolo M, Lamas G (1999). Dual-chamber vs ventricular pacing in the elderly: quality of life and clinical outcomes. Eur Heart J, 20:1607-1608.
8. Rajaeefard A, Ghorbani M, Babaei Baigi MA, Tabatabae H (2015). Ten-year Survival and Its Associated Factors in the Patients Undergoing
Pacemaker Implantation in Hospitals Affiliated to Shiraz University of Medical Sciences During 2002 - 2012. *Iran Red Crescent Med J*, 17:e20744.

9. Koller MT, Schae B, Wolbers M, Sticherling C, Bucher HC, Osswald S (2008). Death Without Prior Appropriate Implantable Cardioverter-Defibrillator Therapy: A Competing Risk Study. *Circulation*, 117:1918-1926.

10. Wolbers M, Koller MT, Witterman JC, Steyerberg EW (2009). Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology*, 20:555-561.

11. Putter H, Fiocco M, Geskus R (2007). Tutorial in biostatistics: competing risks and multi-state models. *Stat Med*, 26:2389-2430.

12. Kalbfleisch JD, Prentice RL (2011). *The statistical analysis of failure time data*. ed. John Wiley & Sons.

13. Tsiatis A (1975). A nonidentifiability aspect of the problem of competing risks. *Proc Natl Acad Sci U S A*, 72:20-22.

14. Grunkemeier GI, Anderson RP, Miller DC, Starr A (1997). Time-related analysis of nonfatal heart valve complications: cumulative incidence (actual) versus Kaplan-Meier (actuarial). *Circulation*, 96:II-70-4; discussion II-74-5.

15. Grunkemeier GI, Jin R, Eijkemans MJ, Takkenberg JJ (2007). Actual and actuarial probabilities of competing risks: apples and lemons. *Ann Thorac Surg*, 83:1586-1592.

16. Ghaem Maralani H, Tai BC, Wong TY, Tai ES, Li J, Wang JJ, Mitchell P (2014). The prognostic role of body mass index on mortality amongst the middle-aged and elderly: a competing risk analysis. *Diabetes Res Clin Pract*, 103:42-50.

17. Barili F, Cheema FH, Barzaghi N, Grossi C (2012). The analysis of intensive care unit length of stay in a competing risk setting. *Eur J Cardiothorac Surg*, 41:232.

18. Deslandes E, Chevret S (2010). Joint modeling of multivariate longitudinal data and the dropout process in a competing risk setting: application to ICU data. *BMC Med Res Methodol*, 10:69.

19. Klein JP, Andersen PK (2005). Regression modeling of competing risks data based on pseudovalues of the cumulative incidence function. *Biometrics*, 61:223-229.

20. Kleinbaum DG, Klein M (1996). *Survival Analysis: A Self-learning Text*. ed. Springer.

21. Pintilie M (2006). *Competing risks: a practical perspective*. ed. John Wiley & Sons.

22. Abadi A, Dehghani-Anari M, Yavari P, Alavi-Majd H, Bajik K (2013). Application of the competing risk models for the analysis of risk factors in patients with breast cancer. *KAUMS Journal (FEYZ)*, 16:546-552.

23. Barili F, Barzaghi N, Cheema FH, Capo A, Jiang J, Ardemagni E, Argenziano M, Grossi C (2013). An original model to predict Intensive Care Unit length-of-stay after cardiac surgery in a competing risk framework. *Int J Cardiol*, 168:219-225.

24. Tai B-C, Grundy R, Machin D (2011). On the importance of accounting for competing risks in pediatric brain cancer: II. Regression modeling and sample size. *Int J Radiat Oncol Biol Phys*, 79:1139-1146.

25. Shen WK, Hammill SC, Hayes DL, Packer DL, Bailey KR, Ballard DJ, Gersh BJ (1994). Long-Term Survival After Pacemaker Implantation For Heart-Block In Patients Greater-Than-Or-Equal-To-65 Years. *Am J Cardiol*, 74:560-564.

26. Ozcan C, Jahangir A, Friedman PA, Patel PJ, Munger TM, Rea RF, Lloyd MA, Packer DL, Hodge DO, Gersh BJ, Hammill SC, Shen WK (2001). Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. *N Engl J Med*, 344:1043-1051.

27. Lamas GA, Orav J, Stambler BS, Ellenhorn KA, Sgarbossa EB, Huang SKS, Marinchak RA, Estes NAM, Mitchell GP, Lieberman EH, Mangione CM, Goldman L, Pacemaker Selection Elderly I (1998). Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. *N Engl J Med*, 338:1097-1104.

28. Lamas GA, Lee KI, Sweeney MO, Silverman R, Leon A, Yee R, Marinchak RA, Flaker G, Schron E, Orav EJ (2002). Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. *N Engl J Med*, 346:1854-1862.

29. Sowers JR1 (2003). Obesity as a cardiovascular risk factor. *Am J Med*, 115 Suppl 8A:37S-41S.