ORIGINAL ARTICLE

Development and External Validation of a Predictive Score of Postoperative Mediastinitis in Cardiovascular Surgery Derived from the XVI CONAREC Multicenter Registry

Desarrollo y validación externa de un puntaje predictivo de mediastinitis posoperatoria en cirugía cardíaca derivado del registro multicéntrico CONAREC XVI

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ABSTRACT

Background: The aim of this analysis was to define independent predictive variables for the development of mediastinitis after cardiovascular surgery and develop a validated score to stratify the risk of its manifestation.
Methods: Data were retrieved from the XVI CONAREC study comprising adults undergoing cardiovascular surgery between September 2007 and October 2008 in 49 centers of 16 provinces in Argentina. Mediastinitis was defined as the presence of clinical signs attributable to the condition or positive cultures. Epidemiological and clinical variables, type of surgery, intraoperative and postoperative variables and complementary tests were evaluated. A multiple logistic regression model was used to identify the independent variables associated with perioperative mediastinitis. A two-tailed alpha error <0.05 was considered statistically significant. A score was built and was externally validated in patients from other surgical centers.
Results: A total of 2,553 patients were analyzed: 1,465 (57.4%) undergoing coronary artery bypass graft surgery, 359 (14.1%) aortic valve replacement, 169 (6.6%) mitral valve surgery, 312 (12.2%) combined surgery and 248 (9.7%) other procedures,. The overall incidence of mediastinitis was 1.88%. The variables associated with the development of mediastinitis were: smoking (OR: 2.3; 95% CI 1.1-5.1; p=0.02), severe left ventricular dysfunction (OR: 2.8; 95% CI 1.3-6.2; p=0.001), reoperation (OR: 4.6; 95% CI 1.8-11.3; p=0.01) and postoperative renal failure (OR: 4.3; 95% CI 1.9-9.6; p=0.0001). A risk score was built assigning 1 point for severe left ventricular dysfunction, 1 point for history of smoking, 2 points for the development of renal failure and 2 points for need for reoperation. The area under the ROC curve for mortality was 0.72 (95% CI 0.64-0.81; Hosmer Lemeshow test p=0.9). The external validation was performed on 1,657 patients with mean age 62.8±13.3 years. The incidence of mediastinitis was 1.6%. The area under the ROC curve for the development of mediastinitis was 0.70 (95% CI, 0.58-0.80; p=0.001).
Conclusions: A predictive score for the development of postoperative mediastinitis after cardiovascular surgery is relevant for daily practice, both for the prevention as for the early detection of this severe complication.

Key words: Cardiac Surgical Procedures/adverse effects - Postoperative complications - Mediastinitis - Predictive Value of Tests - Risk Assessment

RESUMEN

Objetivos: El objetivo de este análisis fue definir variables predictoras independientes para la aparición de mediastinitis poscirugía cardíaca, y desarrollar un puntaje validado para estratificar el riesgo de manifestación de mediastinitis.
Materiales y métodos: Se analizaron datos el estudio CONAREC XVI de adultos sometidos a cirugía cardíaca entre 2007 y 2008, en 49 centros de 16 provincias argentinas. Se definió mediastinitis como la presencia de signos clínicos o cultivos positivos. Se evaluaron variables epidemiológicas, clínicas, tipo de cirugía, variables intraoperatorias y posoperatorias, estudios complementarios. Se realizó un análisis de regresión logística múltiple para identificar variables independientemente asociadas a la manifestación de mediastinitis posoperatoria. Se consideró como significativa un error alfa menor del 5% a dos colas. Se construyó un score y se realizó una validación externa con pacientes de otros centros quirúrgicos.
Resultados: Se analizaron 2553 pacientes: 1465 (57,4%) sometidos a cirugía coronaria, 359 (14,1%) a reemplazo valvular aórtico, 169 (6,6%) a cirugía valvular mitral, 312 (12,2%) a cirugía combinada y 248 (9,7%) a otras. La incidencia de mediastinitis fue 1,88% en la población global. Las variables asociadas al desarrollo de mediastinitis fueron: antecedente de tabaquismo, OR: 2,3 (IC 95%

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1,1-5,1) p = 0,02, disfunción ventricular grave, OR: 2,8 (IC 95% 1,3-6,2) p = 0,001, reoperación, OR: 4,6 (IC 95% 1,8-11,3) p = 0,001, e insuficiencia renal posoperatoria, OR: 4,3 (IC 95% 1,9-9,6) p = 0,0001. Se construyó un score de riesgo adjudicando los siguientes puntajes según la presencia o ausencia de cada una de los cuatros variables del modelo resultante: 1 punto en caso de disfunción ventricular grave, 1 punto para el antecedente de tabaquismo, 2 puntos para el desarrollo de insuficiencia renal y 2 puntos para la necesidad de reoperación. El área ROC para mortalidad fue 0,72 (IC 95% 0,64-0,81) (Hosmer Lemeshow p = 0,9). El grupo de validación incluyó 1657 pacientes con edad media fue de 62,8 ± 13 años. Se observó una incidencia de mediastinitis de 1,6%. El área ROC para desarrollo de mediastinitis fue 0,70 (IC 95% 0,58-0,80), p = 0,001.
Conclusiones: La construcción de un score de riesgo predictivo del desarrollo de mediastinitis en el posoperatorio de cirugía cardíaca resulta relevante para su aplicación en la práctica diaria, tanto para la prevención como para la detección temprana de esta grave complicación.

Palabras clave: Procedimientos quirúrgicos cardíacos/efectos adversos - Complicaciones posoperatorias - Mediastinitis - Valor predictivo de las pruebas - Medición de riesgo

Abbreviations

AMI	Acute myocardial infarction	**DBT**	Diabetes
CABGS	Coronary artery bypass graft surgery	**DLP**	Dyslipidemia
COPD	Chronic obstructive pulmonary disease	**HT**	Hypertension
CRF	Chronic renal failure	**SH**	Smoking habits

INTRODUCTION

Mediastinitis is still an alarming complication in the postoperative period of cardiac surgery, with an incidence ranging between 0.6% and 3.3% and high morbidity and mortality; (1) therefore, early diagnosis and treatment is essential.

The evidence currently available about predictors of mediastinitis in the postoperative period of cardiac surgery is based on reports from single centers or retrospective analyses with unspecific endpoints such as overall postoperative infections. (2-4) Based on this situation, we decided to perform an analysis derived from a multicenter registry (derivation cohort) with the aim of detecting variables independently associated with the development of postoperative mediastinitis after cardiac surgery and build a predictive score performing internal and external validation in another contemporary population (validation cohort).

METHODS

The information analyzed was obtained from the XVI CONAREC study, a multicenter and prospective registry of consecutive patients >18 years undergoing cardiovascular surgery between September 2007 and October 2008 in 49 academic centers with cardiac surgical facilities, distributed in 16 provinces of Argentina. Mediastinitis was defined as the presence of clinical signs attributable to the condition or positive cultures. The complete information about the methods, ethical concepts, participating centers and other definitions used in the study has been previously published. (1) Numerous publications were analyzed to identify the independent variables associated with the manifestation of postoperative mediastinitis in order to build a predictive score. Finally, the score underwent external validation in a group of patients contemporary to the derivation population from other surgical centers.

Statistical analysis

Proportions were expressed as percentages and quantitative variables were analyzed according to their distribution (parametric or non-parametric) and were expressed as mean and standard deviation or median and interquartile range (IQR) 25-75. The chi square test was used to compare proportions, and the Mann Whitney Wilcoxon test and Student's t test to compare quantitative variables with non-parametric and parametric distribution, respectively. The odds ratio (OR) was also calculated with its corresponding 95% confidence interval (95% CI). Preoperative and postoperative variables with a p value <0.1 were included in a logistic regression model by means of a stepwise selection procedure, to identify variables with an independent association with postoperative mediastinitis. Variables with a p value <0.05 were considered independent variables. A score was built using the incidence of postoperative mediastinitis after coronary artery bypass graft surgery (CABGS) with the variables independently associated with this event, and points were assigned to each variable according to the relationship between their partial beta coefficients. The score of each patient was then calculated by adding the points of the respective variables present. The discriminative performance of the score to predict postoperative mediastinitis was evaluated by building an area under the ROC curve. The Hosmer Lemeshow goodness of fit test was used to evaluate the calibration of the score, comparing the proportion of observed versus expected events in the different risk subgroups. SPSS 19 software package (Chicago, Illinois, USA) was used for the statistical analyses..

Ethical considerations

The protocol was assessed and approved by the local Institutional Review Boards which waived the need for an informed consent to use data.

RESULTS

A total of 2,553 patients undergoing cardiac surgery were included between September 2007 and October 2008, distributed as follows: CABGS: 1,465 patients (57.4%), aortic valve replacement: 359 (14.1%), mitral valve surgery: 169 (6.6%), combined surgery (revascularization and heart valve surgery): 312 (12.2%), and other procedures: 248 (9.7%). The general characteristics of the population have been previously pub-

Table 1. Intraoperative and postoperative results in patients undergoing mitral valve repair

Preoperative variables		Mediastinitis		
	Overall	Yes	No	p
Age (years)	62 ± 10	64 ± 10	63 ± 10	
Women (%)	24	24	25	ns
Current smokers, %	38	53	38	0.03
Diabetes (%)	26	30	25	ns
Dyslipidemia (%)	58	58	65	ns
Hypertension (%)	77	76	88	ns
Family history (%)	16	16	25	ns
COPD (%)	9	9	16	ns
Previous AMI (%)	25	31	25	ns
Previous CABGS (%)	1.6	7	1.5	0.03
Previous PCI (%)	12.4	11	12	ns
Previous renal failure (%)	2	0	2	ns
Unstable angina (%)	36	36	37	ns
Stable chronic angina (%)	24	24	20	ns
Heart failure (%)	16	16	11	ns
Cardiogenic shock (%)	0.8	2.3	0.82	ns
Perioperative variables				
Preoperative glycemia (mg/l)	115±41	124±40	115±49	ns
Hematocrit (%)	38±5	38±5	39±5	ns
Creatinine levels (mg/l)	1.01±0.2	1.7±0.3	1.1±0.3	ns
Use of inotropic agents (%)	2.8	2.5	2.3	ns
Use of intraaortic balloon pump (%)	1.6	1	1.6	ns
Preoperative acute renal failure (%)	2.9	2.1	2.2	ns
Severe left ventricular dysfunction (%)	9	15	4	0.002
Emergency surgery (%)	2.1	0	2.2	ns
Type of surgery (%)				ns
CABGS (%)	62%	63	61	ns
CABGS + heart valve surgery (%)	18	17	19	ns
Heart valve surgery (%)	20	21	20	ns
Use of cardiopulmonary bypass (%)	67	81	67	ns
Aortic cross-clamp time, (min)	74	65	74	ns
CPB time (min)	103	99	103	ns
Number of grafts	2.2 1.3	2.4 1.3	2.2 1.2	ns
Use of internal thoracic artery (%)	66	62	66	ns
Use of radial access (%)	9	9.2	4.7	ns
Reoperation (%)	5.5	23	5	0.02
Low cardiac output syndrome (%)	21	30	21	ns
Postoperative renal failure (%)	1.8	3.9	0.2	0.001

COPD: Chronic obstructive pulmonary disease. AMI: Acute myocardial infarction. CABGS: Coronary artery bypass graft surgery. PCI: Percutaneous coronary intervention. CPB: Cardiopulmonary bypass.

lished. Table 1 shows the prevalence of mediastinitis according to the different preoperative and postoperative variables of CABGS. The overall incidence of mediastinitis was 1.88%; it was 1.84% in patients undergoing CABGS, 3.06% in those undergoing aortic valve replacement, 0.59% for mitral valve surgery and 1.6% for combined procedures, p=NS.

Preoperative variables

The following baseline preoperative variables were included in the univariate analysis: history of smoking habits (SH), diabetes (DBT), dyslipidemia (DLP), hypertension (HT), chronic obstructive pulmonary disease (COPD), prior acute myocardial infarction (AMI), CABGS, heart valve surgery and percutaneous coronary artery intervention, chronic renal failure (CRF), previous stroke and peripheral vascular disease, and severe left ventricular dysfunction. The variables associated with the clinical condition were unstable angina, stable chronic angina, syncope on admission, acute heart failure, cardiogenic shock, emergency surgery and EuroSCORE (Table 1).

Postoperative mediastinitis was more common in patients with history of SH, HT, syncope on admission, history of CABGS and severe left ventricular dysfunction.

There was no information about the type of sternal closure, wound stability, sternal dehiscence or use of bilateral internal thoracic artery, known confounders associated with postoperative mediastinitis.

Perioperative variables

The variables analyzed were type of surgery (CABGS vs. valvular surgery) use of cardiopulmonary bypass (CPB) and prolonged CPB time, use of internal thoracic artery, renal failure and need for reoperation. The incidence of mediastinitis was significantly higher in patients reoperated on (OR: 4.9; 95% CI 2.6-9.2; p=0.0001) and in those who developed postoperative renal failure (OR: 5.5; 95% CI 2.6-11; p=0.001), while the use of CPB was associated with a trend toward higher incidence. Yet, there were no differences in the use of grafts with internal thoracic artery, CPB or aortic cross-clamp times and the type of surgery (Table 1).

Association with complications and length of stay

The mean prevalence of sepsis in the population was 4.2%, and postoperative mediastinitis was significantly greater in patients with postoperative sepsis. The prevalence of postoperative sepsis was 3.6% in patients without mediastinitis vs. 39% in those with mediastinitis (OR: 17; 95% CI 9-33; p <0.001). Postoperative hospital stay was 6 days (IQR 2-75: 5.9). The presence of mediastinitis was associated with longer hospital stay: 22 (9-42) days vs. 6 (5-9) days, p <0.0001.

Logistic regression analysis, development of the score and external validation

After performing logistic regression analysis, the preoperative variables associated with the development of mediastinitis after CABGS were SH (OR: 2.3; 95% CI 1.1-5.1; p=0.02), moderate to severe left ventricular dysfunction (OR: 2.8; 95% CI 1.3-6.2; p=0.001), reoperation (OR: 4,6; 95% CI 1.8-11.3; p=0.01) and postoperative renal failure (OR: 4.3; 95% CI 1.9-9.6; p=0.0001 (Table 2).

The points were assigned according to the presence or absence of each of the four variables of the resulting model, proportionally to their regression beta coefficients: 1 (one) point for severe left ventricular dysfunction, 1 (one) point for history of SH, 2 (two) points for development of postoperative CRF, 2 (two) points for reoperation and 0 (zero) points for absent variables. The additive score was calculated by adding the points for each particular case according to the presence or absence of the four variables.

Once the score was developed, internal validation was performed. The discriminative performance of the score to predict postoperative mediastinitis was evaluated by analyzing the area under the ROC curve (0.72; 95% CI, 0.64-0.81; p=0.0001).

The Hosmer Lemeshow goodness of fit test showed acceptable concordance between observed versus expected events (chi square test, 1.92, p=0.5). Figure 1 shows the association between the prevalence of observed versus expected mediastinitis according to the predictive score in all the subgroups. The maximum score for the entire population was 5 points out of 6 points.

The area under the ROC curve for non-coronary cardiac surgery (valvular surgery or combined procedures; n=1,088) was 0.72 (95% CI 0.58-0.85; p=0.0001, Z score: 5.06). The discriminative performance of the EuroSCORE to predict mediastinitis was poor (area under the ROC curve, 0.58; 95% CI 0.49-0.62).

The external validation of the score was performed with a group of 1,657 patients from other surgical centers and contemporary to the derivation population. Mean age was 62.8±13 years; 77% were men and 28% had SH. Severe left ventricular dysfunction was present in 33% of the patients. The incidence of mediastinitis was 1.6%. In the validation group, the area under the ROC curve for the development of postoperative mediastinitis was 0.70 (95% CI 0.58-0.80; p=0.001; Z score: 3.05). The Hosmer Lemeshow goodness of fit test showed acceptable concordance between observed versus expected events (p=0.3). The area under the ROC curve for patients undergoing CABGS was 0.69 (95% CI 0.56-0.80; p=0.004) and 0.72 (95% CI 0.57-0.90; p=0.04) for those undergoing valvular surgery. In both cases, the calibration was satisfactory according to the Hosmer-Lemeshow test (p=0.2 and 0.4, respectively).

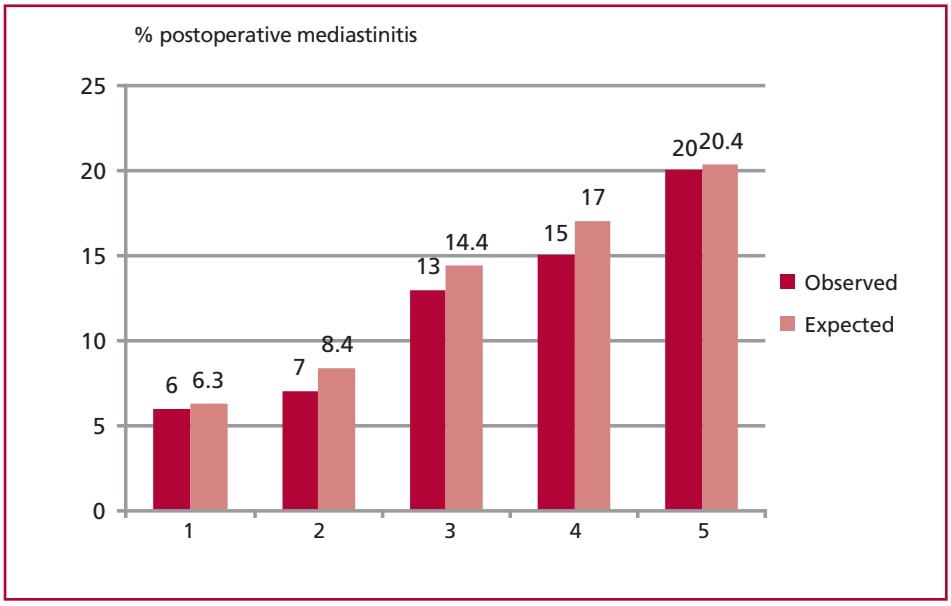
DISCUSSION

In our registry, the incidence of mediastinitis after cardiovascular surgery was 1.8%, similar to the one reported in other series, between 0.6% and 3.3%. (2,

Table 2. Multivariate logistic regression analysis

	B coefficient	Standard error	Wald	OR	OR 95% CI	p
Severe left ventricular dysfunction	0.75	0.33	5.09	2.17	1.1-4	0.002
Reoperation	1.4	0.39	12.9	4.17	1.9-9.1	0.0001
Postoperative renal failure	1.39	0.33	17.2	4.04	2.1-7.8	0.0001
Smoking habit	0.73	0.31	5.4	2.09	1.1-3.8	0.02

Table 1. Percentage of observed versus expected postoperative mediastinitis according to the predictive score for mediastinitis



5) This variability may be explained by the different definitions of mediastinitis used by reports.

While previous publications were based on retrospective analyses or single-center populations, this analysis was made using information of consecutive surgical cases from a multicenter registry. Four independent predictors were identified in our study: two corresponded to preoperative variables -previous ventricular dysfunction and history of SH- and the other two to postoperative variables -renal failure and need for reoperation.

History of SH, but not COPD, was independently associated with the development of mediastinitis. In fact, previous reports have found that the association between SH and surgical site infection may reach up to 12%. (6) The same trend was observed by Gravante et al., who detected that smokers had higher risk of postoperative infections after noncardiac surgeries. This risk was between 3.8 and 14 times greater compared to non-smokers, depending on the length of exposure to tobacco and the number of cigarettes smoked (8.5 pack-years). (7, 8) Likewise, in the present study SH was associated with increased risk of developing mediastinitis after cardiac surgery.

The vasodilator and microvascular endothelial permeability effects (9, 10) of tobacco smoke components (such as nicotine, nitric oxide and carbon monoxide), the reduction of oxygen-carrying capacity and procoagulation induced by increased levels of carboxyhemoglobin (9-11) may partly respond to the pathophysiological mechanism explaining this association. Coughing in the postoperative period may also be a hidden confounding variable which also plays an active role in this situation.

In a retrospective analysis, Thakar et al. (13) demonstrated the value of acute renal failure as an independent predictor of infections after CABGS. In the same sense, Magedanz et al. (4) found that reoperation was independently associated with mediastinitis after CABGS, with an OR of 3.9 (95% CI 2-7.9).

There are no specific reports to explain the association between left ventricular dysfunction and mediastinitis. As a related report, Tang et al. found a clear association between history of heart failure and postoperative myocarditis. (14)

Previous studies identified other independent predictors of mediastinitis, different from our findings. In a retrospective analysis of 1,700 patients, Diez et al. identified three variables as predictors for the development of mediastinitis: increased body mass index, COPD and use of bilateral internal thoracic artery for CABGS. (15) Magedanz et al. reported similar findings in a single center prospective cohort of 2,809 patients undergoing CABGS (either isolated or combined procedures), identifying COPD, obesity, need for reoperation, transfusions and unstable angina as predictors of mediastinitis. (4) Increased body mass index was associated with mediastinitis in previous studies; (7, 8) this was attributed to differences in the pharmacokinetics of antibiotics due to increased amount of fatty tissue and technical difficulties in maintaining sterility. Paradoxically, the study did not show any association with mediastinitis, probably due to differences in the patients included.

Study limitations

The limitations related to the fact that all the participating centers were academic institutions and that patients were followed-up only during hospitalization have been previously published. (5) As the primary aim of the registry was not focused on mediastinitis, we lacked relevant data about infections, as the results of blood cultures or perioperative treatment with antibiotics. The use of bilateral internal thoracic ar-

tery for CABGS, a strategy that, according to some authors, could be associated with the development of postoperative infections, was not available. (1)

CONCLUSIONS

This simple score, derived from an Argentine multicenter registry and validated in an external population, allows estimating the risk of developing a severe complication as postoperative mediastinitis after cardiovascular surgery. This interesting observation serves as a hypothesis generator that should be prospectively tested in our setting in different centers. Above all, the score is useful for taking preventive measures related to surgical strategies, such as control of perioperative bleeding that leads to reoperations, among others.

Conflicts of interest

None declared. (See authors' conflicts of interest forms on the website/Supplementary material).

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