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Risk Factors for Developing Surgical Wound Infection following Coronary Artery Bypass Graft Surgery, in Armenia

(A Case-Control study)

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Table of Content

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Abbreviation list

BMI - body mass index

CABG - coronary artery by pass graft surgery

CAD - coronary artery disease

CDC - centers for disease control and prevention

CI - confidence interval

CVD - cardiovascular disease

HAI - hospital acquired infection

ICU - intensive care unit

NMMC - Nork-Marash Medical Center

OR - odds ratio

SSI - surgical site infection

WHO - World Health Organization

Abstract

Background: Sternal and leg wound infections following coronary artery bypass graft surgery (CABG) surgery are risk factors for increased morbidity and mortality as well as cost of treatment. It is estimated that the average cost of maintaining a patient in the hospital with a sternal wound infection is three times higher than the cost of maintaining a patient with an uncomplicated postoperative result. Deep sternal wound infection has been reported to occur in 1% to 4% of patients after CABG and carries a mortality of nearly 25%. Surveillance of surgical site infection (SSI) in hospitals in England between October 1997 and September 2002 showed that 4.3% of the patients developed SSI following CABG. According to a study conducted from 2003 to 2006 in Nork-Marash Medical Center (NMMC) in Yerevan, Armenia, the incidence of wound infections after CABG in NMMC was 7.4%.

Objective: The overriding objective was to assess the combined effect of risk factors for developing wound infection following CABG, controlling for potential confounders.

Design: A retrospective unmatched case-control study was conducted. Data were abstracted from medical records.

Study population: The CABG patient population from Nork-Marash Medical Center who underwent CABG from January 1, 2006 through March 31, 2009.

Results: The sample size was 801 (128 cases and 673 controls). The overall wound infection rate over the course of the hospital stay was 7.5% (128/1704). Among wound infection cases with reported sites of infection (out of 128 cases, seven were missing data on site of infection), the percent of patients developing chest infection alone was 65.3(79/121) %, the percent of developing leg infection alone was 28.9(35/121) %, and 5.8(7/121) % of patients developed both chest and leg infections. Staphylococcus Epidermitis (59.2% out of all cases), Staphylococcus Aureus (23.1%) and Escherichia Coli (12.9 %) were the most common infectious pathogens. The mean age of participants was 57 years. About 86% of all participants were male. The mean duration of operation was 4.3 hours, the mean duration of artificial breathing time was 23 hours and the mean duration of stay in the intensive care unit (ICU) was 67 hours. Bivariate analysis found that the unadjusted OR for developing SSI among those having diabetes compared to not having diabetes was 2.93 (95% CI: 1.9-4.4), the unadjusted OR for females as compared to males was 2.3 (95% CI: 1.4-3.8), and for those using versus not using inotropic drugs was 2.39 (95% CI: 1.3-4.2). Bivariate analysis of continuous variables showed that BMI (p-value <0.001), duration of operation (p-value <0.001), artificial breathing time (p-value <0.001), intubation time (p-value <0.001, duration of stay in the ICU (p-value <0.001), and blood glucose level (p-value <0.001) were associated with increased risk for developing wound infection following CABG. The final predictive multivariate model found the likelihood of developing wound infection was higher among those who had longer duration of operation, longer duration of stay in the ICU, who had diabetes, higher BMI and were female. A statistically significant interaction included in the final model was found between duration of operation and duration of stay in ICU (p=0.018), an interaction which suppressed their individual combined effects.

Conclusions: Important predictive risk factors for increased risk of wound infection following CABG were longer duration of operation and stay in the ICU, diabetes, higher BMI and being female. Further research is needed to evaluate monthly/seasonal effects on rates of CABG wound infections and to evaluate rare risk factors utilizing larger sample sizes.

Introduction

Hospital Acquired Infections (HAI)

According to the World Health Organization (WHO) definition, *hospital acquired infections* or nosocomial infections are infections acquired by patients in hospitals or other health care facilities for which the infection was not present at the time of admission(1;2). The Centers for Disease Control and Prevention (CDC) define an HAI as "a localized or systemic condition that results from an adverse reaction to the presence of an infectious agent(s) or its toxin(s) and for which there was no evidence the infection was present or incubating at admission(3;4)."

The risk factors for HAI are numerous. One of the most important risk factors for HAI worldwide is immuno-compromised status, which weakens the patient's resistance against infections(1). In addition, the overuse of antibiotics often leads to antibiotic-resistant pathogens that further increase the risk of HAI(1;2).

HAI is a major public health problem throughout the world; it is one of the major causes of morbidity and mortality and elevates the cost of hospital care(1;2;5-10). This problem is expected to increase in hospitals throughout the developing countries due to increasingly crowded facilities, aging populations, and changing patterns of illnesses and treatments(1).

Incidence of HAI

Though the incidence rates of HAI vary between hospitals, it is estimated that 10% of hospital patients worldwide develop HAI(1). Different studies show that in developing countries about 5% to 15% of all hospitalized patients develop HAI(10). In the United States in 2001, deaths associated with HAIs exceeded the number of deaths attributed to some of the top ten leading causes of death (e.g. diabetes mellitus caused 71,372 deaths, being ranked sixth in the list of ten) reported in U.S vital statistics in 2001(11-13). In a WHO publication

published in2002, it was reported that the highest incidence rates of HAI were observed in hospitals in the Eastern Mediterranean Region with 11.8% of all patients(1). It was estimated that annually around 40,000 deaths (about 12.1% of death in hospitals) in Germany are attributable to infections acquired in the hospital(14).

HAIs are also a major financial and social burden on families and health systems. HAIs in the U.S. were estimated to cost $17-29 billion annually(10). In Thailand, HAI cost more than US$ 40 million every year(1).

Types of Hospital Acquired Infection

There are several types of HAIs based on the body site and patient exposures (2;3;14;15). According to Klevens et al. the four most common types of HAIs in U.S. hospitals in 2002 are urinary tract infections (32% of all HAI's), *surgical site infections (SSI)* (22 %), lung infections (15%), and bloodstream infections (14%). Other less frequent HAIs include bone and joint, central nervous system, cardiovascular, eye, ear, nose, throat, mouth, gastrointestinal, reproductive tract, skin and soft tissue and systemic infections (totaling 17%) (13). A WHO publication describes a similar distribution of HAI sites based on a French national prevalence survey in 1996 (see appendix 1) (2). These studies show that SSI is one of the most frequent types of HAI (2;13). In the reviewed literature the SSI is the second or third most common healthcare-associated infection causing significant public health problems which limit the potential benefits of surgical interventions(1-4;12-14).

Incidence Rate of Surgical Site Infection

The definition of SSI is mainly clinical: The purulent discharge around the wound or the insertion site of the drain, or spreading cellulitis from the wound is identified as SSI(2). The infection is usually acquired during the operation itself either from air, medical equipment, surgeons and other staff, or from pathogens on the skin or in the operative site. SSI is the most common complication following surgery. Different studies show that the

incidence rate of SSI varies from 0.5 to 15% of surgeries, depending on the type of operation and the patient health status(2;16-20). Surveillance of SSI in English Hospitals, between October 1997 and September 2002, shows that the highest rates of developing SSI follow bile duct, liver, pancreas surgeries (12.3 percent) and Limb amputation (15.6 percent)(18).

Prevention of Surgical Site Infection

There are several methods for preventing SSI. One proven infection control intervention is infection surveillance followed by prompt effective treatment. Surveillance includes understanding patient and care risk factors and incidence rates of infection. Surveillance allows the tracking of trends of infections for increases or decreases in incidence rates, identifying clusters of infection, comparing institutions and specializations and evaluating the effectiveness of infection control measures (3;12;16;16;18;21). CDC recommends routine surveillance for some HAIs, including SSIs (22).

CABG Surgery

Coronary Artery Bypass Graft (CABG) surgery is the most common operation that cardio-thoracic surgeons perform for the treatment of coronary artery disease (CAD) worldwide(12;23). Cardiothoracic surgeons perform CABG to bypass blockages or obstructions of the coronary arteries. CABG procedures are performed by revascularization of the heart using the internal mammary artery, peripheral veins or a combination of both types of grafts (23). CABG is performed under general anesthesia. Patients with CAD who are the most frequent candidates for CAGB almost always have other comorbidities (such as diabetes, high blood pressure, renal failure, hepatic failure, etc.) that can lead to complications with non-desired outcomes. Depending on many risk factors, CABG mortality rates can range from 1% to 20%(23). One of the important complications of CABG is SSI(12;24-28).

Incidence of SSI Development following CABG

The development of sternal and leg wound infections associated with CABG is a risk factor for increased morbidity and mortality, and increases the cost of treatment. Surgical wound infections can lengthen treatment with antibiotics, require additional surgery or both. It is estimated that the average cost of maintaining a patient in the hospital with a sternal wound infection is about three times higher than the cost of maintaining a patient with an uncomplicated postoperative result (12;24-28). In the review of CABG studies the reported incidence of SSIs varies (12;24-28). Deep sternal wound infection has been reported to occur in 1% to 4% of patients after CABG and carries a mortality of nearly 25% (12;24-28). Surveillance of SSI in English Hospitals, between October 1997 and September 2002, shows that the 4.3 percent of the patients develop SSI following CABG (18). A study conducted in 35 hospitals in New York City in U.S. during the period January 1, 2007 to March 31, 2007 show that the SSI rate following CABG was 3.4%(12). According to a study conducted from 2003 to 2006, in Nork-Marash Medical Center (NMMC) in Yerevan, Armenia, the incidence of wound infections following CABG in NMMC was 7.4% (27).

CAD and CABG in Armenia

As in most countries, cardiovascular diseases (CVD) are the leading causes of death in Armenia. According to the *Demographic Health Survey* 2005 in Armenia, 58% of all deaths in 2003 (WHO, 2006a) were due to CVD (29). It was estimated that, in Armenia, 61% of all cardiovascular disease deaths are due to CAD (30;31). It is also estimated that, on average, approximately three CABG procedures are performed every two days at the NMMC in Yerevan, Armenia for treatment of CAD.

Risk Factors for SSI Development following CABG

Staphylococus aureus, Coagulase-negative staphylococci, Enterococcus, and Escherichia coli are the most common pathogens isolated during CABG surgery (12;27;32-

37). Most wound-infecting pathogens are believed to infect at the time of surgery. A substantial proportion of surgical wound infections are attributed to external contamination. External contamination may come from any healthcare personnel or heath facility environmental source, although contact with the wound by the surgical team is probably the most common cause of contamination (12;27;32-37).

Many authors have investigated risk factors for the development of wound infections. The potential risk factors for developing sternal or leg infection are classified into three groups(12;27;32-37). The first group is **preoperative** factors. These risk factors include demographic factors (age, gender, weight, height, body mass index (BMI), and smoking) and risk factors pertaining to medical history (diabetes, hypertension, use of antibiotics, chronic obstructive pulmonary disease, peripheral arterial occlusive disease, previous cardiac surgery, and obesity). Also, preoperative factors consist of post-hospitalization parameters, which include admission to the intensive care unit before surgery and length of stay in intensive care unit, use of steroids, lung function, left-side ejection fraction, right-side ejection fraction, albumin concentration and creatinine concentration. The second group is **intraoperative** factors. These factors include urgency of surgery, operating room, surgical team, surgical procedure, duration of surgery, use of an internal mammary artery, total bypass time, aortic clamp time, blood loss, use of left ventricular assist devices, blood transfusion, blood transfusion materials, cardiac massage, inotropic support and complications. The third group is **postoperative** factors. These factors include duration of artificial breathing and length of stay in the intensive care units after cardiac surgery(12;27;32-37).

Rationale of the study

The Nork-Marash Medical Center is the largest cardio-surgery medical service in Armenia and it serves the entire Armenian population as well as patients from other countries. Still, SSI following CABG occurs in NMMC and results in increasing mortality

and morbidity of patients. The Center provides a rich source of data for investigating risk factors and their associations for developing wound infections following CABG.

Only one prospective largely study of risk factors for infection following CABG previously was conducted in Armenia at the Nork-Marash Medical Center from 2003 to 2006. After 2006, the new methods of prevention of SSI were implemented in NMMC, and it could be interesting to see if there are changes during this time-period related to risk factors for SSI development following CAGB. It would be helpful to compare results of this study with the previous ones. The prior study conducted in NMMC assessed risk factors for infection following CABG and focused on individual risk factors but not on interactions between risk factors (such as diabetes and smoking, or diabetes and BMI).

Aims and Research Questions of the Study

The aim of this proposed study, based on medical record extraction, is to evaluate risk factors for SSI following CABG and assess effect modifications between risk factors in order to find ways to modify risks and reduce the rates of adverse outcomes.

The aims of the study are:

- To identify risk factors for development of SSI following CABG among the Armenian population
- To identify interactions between risk factors for development of wound infection following CABG among the Armenian population
- To identify factors that can be used for early detection of wound infection following CABG among the Armenian population
- To develop recommendations for guidelines to predict, prevent and to improve early detection of wound infection following CABG among the Armenian population

The research questions of the study include:

- What are the independent risk factors for developing wound infection following CABG among the Armenian population?
- What are the interactions between risk factors for developing wound infection following CABG?
- What are the risk factors associated with duration of time from CABG surgery to development of wound infection?

Methods and Materials

Study Design and Objectives

To assess risk factors for SSI development as well as to answer the above mentioned research questions, a retrospective unmatched case-control study with 128 cases and 673 controls was conducted. The overriding objective was to assess the combined effect of risk factors for developing wound infection following CABG, controlling for potential confounders during the time-period from January 1, 2006 through March 31, 2009, for the patients of NMMC.

The case control study design is relatively less time consuming for examination of a rare outcome with multiple exposures (38). So the case-control study design was selected because SSI is relatively rare following CABG surgery, and there were multiple exposures to examine.

Study Population

The target population was the Armenian population; the Nork-Marash Medical Center (NMMC) serves almost the entire Armenian population, with few exceptions.

The study population was the CABG patient population from NMMC who underwent CABG from January 1, 2006 through March 31, 2009. During this period 1704 CABG procedures were done.

Definition of Cases

Cases were those CABG patients from the study population (who underwent CABG from January 1, 2006 through March 31, 2009) who developed wound infection before the patient's complete recovery within the hospital stay. In NMMC, postoperative wound inspection of patients was performed every day. If the wound had any signs and symptoms of complications such as erythema, edema, inflammation, pus, or increased pain, a smear was taken from the wound for the culture testing. If the test of smear for bacterial growth is positive the wound is considered as infected, and the patient receives more aggressive treatment with antibiotics.

Definition of Controls

Controls were selected from the study population of patients (who underwent CABG during the period from January 1, 2006 through March 31, 2009) and who did not develop wound infection.

Inclusion Criteria

- Patients of Nork-Marash Medical Center
- Patients who had CABG surgery during the period of January 1, 2006 through March 31, 2009

Exclusion Criteria

- Residency outside of Armenia
- Nationality other that Armenian
- Patients who were missing their medical records
- Patients whose smears were taken but results were not recorded
- Patients who died before completely recovery, not due to SSI, within 30 days after the surgery. SSI infection occurs within 30 days after the operative procedure(1;3).

Sample Size

Sample size calculation was done using EpiInfo StatCalc for unmatched case-control studies (39). It is well known fact that diabetes is a risk factor for developing SSI wound infections (1;2;12;27;37). Because of this diabetes was selected as the exposure for its public health importance and expected difference in proportion between cases (CABG with infection) and controls (CABG without infection). The estimated proportions (35.5% for cases, 22.0% for controls) were based on previous data from the study for Nork-Marash Medical Center CABG infections, assuming a two-sided significance level of 0.05 and 80% power with 1:4 ratio of cases to controls(27). The final sample size was calculated to be 114 cases and 457 controls for a total of 571 records to be abstracted. However, in order to account for missing data, the total number of medical records reviewed was inflated and totaled 801 (128 cases and 673 controls).

Data Collection/ Sampling Frame

Secondary data collection was conducted based on medical record abstractions. CABG patient medical records for the period of time from January 1, 2006 through March 31, 2009 in NMMC were used as the sampling frame with selection of the study population through stratified simple random sampling, stratified by cases and controls. The data were abstracted from the three different types of medical records of the patient. These medical records are medical history, medical form and results of smear test if smear was taken. Due to the small number of cases, all of the cases were selected from the frame (128). The controls (673) selected randomly by the help of "Random Number Generator for the Excel, version 2.0.2."

Study Variables to be Abstracted from Patient Medical Records

Dependent variables:

- Presence or absence of wound infection
- Duration of time from CABG to detection of wound infection

Independent variables:

Presence or absence of diabetes, gender, use of inotropic drug, emergency/urgency of surgery, cardio pulmonary bypass (CBP), smoking status, presence or absence of hypercholesterinemia, presence or absence of gastrointestinal track diseases, presence or absence of respiratory diseases, presence or absence of peripheral vascular diseases, presence or absence of urinary track diseases, age (in years), preoperative hospital stay days, body mass index (BMI) (kg/m^2), duration of operation (in hours), artificial breathing duration (in hours), intubation duration (in hours), duration of stay in ICU (in hours), duration of CBP (in hours), aortal clamp duration (in hours), albumin concentration (mg/dl), blood glucose level (mg/dl).

Data Management/Data Entry

As was mentioned the data collection was based on abstraction of medical records. Abstraction from the medical records included all the variables identified in the different studies for investigation of SSI following CABG that were possible to collect.

The data entry was done directly from the medical records in order to reduce the data collection bias. Electronic forms were developed using Microsoft Access (see appendix 2) and data entry from the medical record was done using Microsoft Office Access software. Then data were transferred to the SPSS 17.0 and STATA 10 statistical softwares for data cleaning and analysis

Statistical Methods/Analysis

All the analyses were done using STATA 10 and SPSS 17 statistical software. After conducting basic descriptive statistics for both cases and controls (means, medians, standard deviations, frequencies) the chi-square test was used to compare differences in proportions of independent variables between infected and not infected groups (between cases and controls). In order to assess the strength of association between each independent variable and the dependent variable, simple logistic regression was performed. Multiple logistic regressions were used to measure the strength of associations between the independent variables and the dependent variable (wound infection versus no wound infection). Multiple logistic regressions were also used to test for effect modifications while controlling for potential confounders.

Ethical Considerations

The study was approved by the Institutional Review Board/Committee on Human Research within the College of Health Sciences at the American University of Armenia. No personal identifiers (such as name, phone number, address) about participants were abstracted or collected. The simple random sample of control participants was identified by random numbers, which were maintained only by the student researcher. Paper abstraction forms were not used for data entry. The collected electronic data will remain secure with access only by the student researcher and will be deleted after publishing findings or within 5 month after finishing the study.

Study Timeframe

The study was conducted over a 4-month period. It started in mid-March 2009 and finished in mid-July 2009. Analysis of the data was completed in July. Based on the analysis and the results, in July the research report was written and prepared for oral presentation.

Results

Quality of the Data

The medical records of all cases were found. From the list of randomly selected controls, 37 medical records of controls were not found or were excluded based on the exclusion criteria. After finishing data collection, it was discovered that different variables had different amounts of missing values. There did not appear to be any systematic biases associated with these missing values, except for the variable “using inotropic drugs”. Because 81% of the missing values for this variable were from year 2006. Missing data constituted about 5% of observations for most variables. In order to increase the validity of the final model, variables with more than 5% missing values (such us “using inotropic drugs”) were not included in the final analysis.

Descriptive Data

A total of 1704 CABG procedures were performed during the study period. The study sample size was 801 (128 cases and 673 cases). A census of hospital post-CABG wound infection rates and numbers, stratified by infected site (chest or leg) and by year, out of *all* the patients who underwent this procedure from January 1, 2006 through March 31, 2009 are provided in table I. The total surgical wound infection rate for chest infection is higher than leg infection. The total wound infection rate was 7.5% (128/1704) for the study time-period. Among wound infection cases with reported sites of infection (out of 128 cases, only seven were missing data on site of infection), the percent of patients developing chest infection alone was 65.3% (79/121), the percent developing leg infection alone was 28.9% (35/121), and 5.8% (7/121) of patients developed both chest and leg infections. Similar to table I the rates and numbers of surgical wound infection, stratified by time periods (3-month time periods) and by different months, among all patients and patients in the sample undergoing this procedure are given in table II and Figure 1 respectively. The estimated wound infection

rate varied across different time-periods. The highest rate for a 3-month periods was 13% between October 1, 2006 and December 31, 2006, and the lowest rate was 4.6% between October 1, 2008 and December 31, 2008 (Table II). Figure 1 shows that the rate of developing SSI infection following CABG appears to peak in May, July and October across years. This suggests that the time of year may also be a predictor for SSI development following CABG.

The pathogens isolated from the wound of patients are listed in table III. Staphylococcus Epidermitis (59.2%), Staphylococcus Aureus (23.1%) and Escherichia Coli (12.9 %) were the most common pathogens.

The mean age of participants was 57 years. About 86 % of participants were male. The mean duration of operation was 4.3 hours, the mean duration of artificial breathing time was 23 hours, the mean duration of being in ICU was 67 hours, and the mean time for detection of infection after surgery was approximately 20 days. Study patients included in the sample had various co-morbidities, such as diabetes (about 28%), hypertension (about 68%), respiratory disease (about 14%), peripheral vascular disease (about 12%), urinary tract disease (about 22%) and gastrointestinal disease (about 45%). Approximately 39% of the study patients were current smokers, 36% were former smokers and 25% of patients never smoke.

The distributions of categorical and continuous characteristics of risk factors for the study population are summarized in table IV and table V, respectively.

Risk Factor Analysis

Unadjusted (chi-square, t-tests, *Mann-Whitney test*) and adjusted (multivariate logistic regression) analyses were performed to investigate the association between wound infection and different risk factors.

Unadjusted Analysis of Risk Factors

Chi-square analysis of the associations between each of the dichotomous independent variables and development of wound infection following CABG are summarized in table IV. Statistically significant associations were found between SSI development and three independent variables (diabetes, female gender and using inotropic drugs). The estimated unadjusted odds ratio (OR) for the association between SSI and diabetes was 2.93 (95%, confidence interval (CI): 1.9-4.4). This means that the odds of SSI development among diabetics are 2.93 times higher than to non-diabetics. The estimated crude OR of the association between SSI and female gender is 2.3 (95% CI: 1.4-3.8), indicating that the odds of SSI development among women are 2.3 times higher as compared to males. The patients using inotropic drugs had 2.39 higher odds for developing SSI as compared to patients who do not use inotropic drugs ($OR_{\text{using-inotropic}}$=2.39, (95% CI: 1.3-4.2)).

The distributions of continuous characteristics were examined by the help of a QQ plots to test normality. The QQ plot examination showed that age and BMI were the only variables that are approximately normally distributed (figure 2 and figure 3). Thus, the mean difference between cases and controls for BMI and age was tested using a *t*-test assuming unequal variances. For the other continuous variables, the median difference was tested by non-parametric *Mann-Whitney test* for independent samples. Table V shows the results of these unadjusted analyses.

Higher BMI (*p*-value <0.005), duration of operation (*p*-value <0.001), artificial breathing time (*p*-value <0.001), intubation duration, duration of stay in ICU (*p*-value <0.005), and blood glucose level (*p*-value <0.001) were the statistically significantly continuous risk factors for the development of wound infection following CABG.

Testing for Confounding

Simple logistic regression analysis was used to identify potential confounders and interactions for the relationships between potential risk factors and wound infection. The results of this analysis showed that potential confounders (age, gender, BMI, using inotropics) were not statistically significantly associated with potential risk factors of interest, nor were they associated with the development of SSI following CABG. This analysis found no confounding effects.

However, multivariable analysis showed confounding by gender of the relationship between smoking and development of SSI. In the multiple logistic regressions adjusting for diabetes and smoking, smoking was not statistically significant, but it became statistically significant when further adjusted for gender. Thus gender confounds the effect of smoking on the development of SSI following CABG (Appendix 3).

Testing for Interactions

Interactions between independent variables were checked, with only two statistically significant interactions being identified: between diabetes and smoking and between duration of operation and duration of stay in the ICU, respectively, on the development of SSI. According to the results of these analysis, the odds for developing SSI following CABG was 2.6 ($p=0.031$) times higher among smoking diabetics as compared to non-smoking diabetics. The odds of developing SSI following CABG was 0.998 ($p=0.014$) times less than expected with every one hour longer operation and with a one hour increase of stay in the ICU (Table V, Appendix 3).

Testing for Correlations between Variables

In order to reduce collinearity, the variables were tested for correlations by excluding one of the pair of correlated variables from the model. The only highly correlated variables were duration of artificial breathing and intubation time. The Pearson's correlation coefficient

for these tow variables was equal to 0.9647. Usually extubation was performed after 10 to 15 minute or just after a patient starts breathing by himself. Therefore, intubation time highly correlated with on the duration of artificial breathing. For this reason, artificial breathing time and intubation time were not included in the same model at the same time (Appendix 3).

Multiple Logistic Regression Analysis

Multiple logistic regression analyses were performed to identify the final predictive model for SSI development following CABG. Initially backward elimination approach (based on p-values) was used to identify variables for inclusion in the final model. The result of this approach found that diabetes, gender, smoking, BMI, duration of stay in the ICU and using inotropic drugs were independent risk factors for developing wound infection (Table VII, Appendix 3).

Model 1
Ln odds (*infection***)** $= \beta_0 + \beta_1$ *diabetic* $+\beta_2$ *gender* $+\beta_3$ *smoking* $+\beta_4$ *BMI* $+\beta_5$ *ICU-time* $+\beta_6$ *using of inotropics*

The second model was developed by including only statistically significant variables, confounders and interaction terms, excluded variables with 5% or more missing values. The sample size of this model was 749, which allows the results of this model to be more generalizable. This model included diabetes, gender, BMI, duration of operation, ICU stay time, and the operation-duration*ICU–time interaction term (Table VIII, appendix 3).

Model 2
Ln odds(*infection***)** $= \beta_0 + \beta_1$ *diabetic* $+\beta_2$ *gender* $+\beta_3$ *BMI* $+\beta_4$ *operation-duration* $+\beta_5$ *ICU-time* $+\beta_6$ *operation-duration*ICU -time*

Descriptive analysis revealed that rates of infection were different in different months and in different 3-month time-periods. Therefore, it was possible that month is a predictor for SSI development following CABG. It was also possible that the time-period when CABG

surgery was conducted was associated with the outcome. To adjust for time of year of surgery the third model included month of surgery (as a dummy variable) and the fourth model included 3-month seasonal periods (as a dummy variable) (Appendix 3).

Model 3
Ln odds(*infection***)** $= \beta_0 + \beta_1$ *diabetic* $+\beta_2$ *gender* $+\beta_3$ *BMI* $+\beta_4$ *operation-duration* $+\beta_5$ *ICU-time* $+\beta_6$ *operation-duration*ICU –time* $+\beta_{7\text{-}17}$ *month*

Model 4
Ln odds(*infection***)** $= \beta_0 + \beta_1$ *diabetic* $+\beta_2$ *gender* $+\beta_3$ *BMI* $+\beta_4$ *operation-duration* $+\beta_5$ *ICU-time* $+\beta_6$ *operation-duration*ICU –time* $+\beta_{7\text{-}13}$ *3-month time periods*

The sample sizes of the 2nd, 3rd and 4th models were equal which allows comparisons across these models. The 2nd model included statistically significant terms only. After adjusting for the variables outlined above, the ORs and significance levels were approximately the same as other multivariable analyses. For this reason, the 2nd model was selected as the best predictive model. The Hosmer-Lemeshow test statistic of the final model is equal to 9.7 with df=8 and Prob.chi2=0.29. This shows that the model has good calibration.

To answer the research question of whether there is a difference between times to detection of infection development between different groups of patients (male vs. female, diabetic vs. non-diabetic etc.) Kaplan-Meier survival analyses were conducted. No factor was found to be statistically significantly associated with duration of time from CABG surgery to time of detection of wound infection.

Discussion

The current study measured associations between risk factors for developing wound infection following CABG in the NMMC among Armenian patients.

A previous study conducted in NMMC from 2003 to 2006 reported a 7.4% rate of developing SSI following CABG, out of which 54.8% were chest infection alone, 41.9% were leg infection alone and 3.2% had developed both leg and chest infection. The current

study found that the incidence of SSI following CABG from 2006-2008 was 7.3%, out of which (excluding the 7 cases with missing data on wound site) the percent of patients developing chest infection alone was 66.7% (72/108), the percent for leg infection alone was 27.8% (30/108), and having infections in both sites was 5.6% (6/108). In the current study, the percent of all leg infections (27.8%+5.6%) out of all wound infections following CABG decreased by 25.9% from the previous study (41.9%+3.2%). This percent reduction may have occurred because, subsequent to 2006, leg wounds were closed immediately after vena harvesting; prior to this change in procedure, these wounds had longer exposure to the surgical surroundings. This method was implemented to decrease the duration of wound exposure to reduce the likelihood of contamination. These particular rates were calculated after excluding the first three month of 2009 because of possible seasonal variability in rates and because of possible incomplete enumeration of the denominator due to medical records not yet having been submitted during those three months (thus not being included in the study frame). Smear test results were complete for all time-periods. The reasons for the corresponding increase in rate of sternal infections from the previous research period to the current research period are unknown and require further research.

Based on a review of the published literature, only the previous study and this current study, both conducted in the NMMC, examined the influence of monthly or seasonal effects on CABG wound infection rates. The previous study found that the infection rate increased in August. This study suggested that this high August rate might be due to construction in the hospital, which reportedly peaked around August. The current study consistently found wound infection rate peaks in May, July and October (Figure 1). These peak rates all correspond to maximum construction periods at the hospital. Another possibility for increased wound infections for these months may be related to the increased number of visits to patients by relatives and friends during the summer months.

The findings from the final multivariable logistic model for developing surgical wound infection following CABG suggest that the risk of developing wound infection is higher among patients having diabetes, among females, for those patients having a longer duration of operation and for those patients having a longer duration of stay in the ICU. Three risk factors of patient characteristics for SSI included having diabetes, higher BMI, and being female. These findings are in agreement with previously published findings in international settings and with the study previously conducted in NMMC (12;27;35;36). However, in contrast, a few studies suggested that males have higher risk for developing infection following CABG than females (Borger M.A. et al. (1998), Roy M.C. (1998), Eklund A.M. et al. (2006)). Why women are at greater risk than men in Armenia for wound infection requires further study.

BMI is an independent risk factor for developing wound infection. People with higher BMI typically have more adipose tissue, which makes surgery technically more difficult and may lead to more aggressive and prolonged surgery. In addition, the wound surface is greater among people with higher BMI, potentially increased the likelihood of wound infection.

Having diabetes was another independent risk factor for developing wound infection. This is consistent with findings in the published literature. Diabetes reduces humoral and cellular immunity and prolongs healing, potentially increasing risk of infection.

The final model also found an interaction between ICU time and operation time. After taking into account this interaction through a linear combination with duration of surgery, the average expected increase in odds for wound infection, though still increasing, was slightly reduced in magnitude. A possible explanation for this interaction is that longer duration of operation with less duration of ICU time suggests that this patient had better recovery, decreasing the probability of developing wound infection.

Though not included in the final multivariable model because too many of the records were missing data, findings on smoking and using inotropic drugs were consistent with other published findings. Both were associated with increased risk of wound infection.

The frequencies of recovered pathogens are consistent with the findings of other researchers and it appears that S. aureus, S. epidermitis and E. coli were found to be the most common pathogens causing CABG related SSI.

Study Limitations

The medical records did not consistently document albumin concentration, chronic obstructive pulmonary diseases and the use of isotropic drugs, thus the study could not assess their associations or their combined associations in the final predictive multivariable logistic regression model. Records for patients during the first three months of 2009 probably did not include a complete list of all operated patients because their CABG surgeries were so recent at the time of the current study data collection. Thus, for these three months, overall rates may be somewhat biased, though this would not bias the associations between risk factors and risk of wound infection nor would it bias time from surgery to detection of wound infection. For calculating overall wound infection rate for comparison to prior rates, these last three months of the study period were excluded. Another source of bias may be associated with records that were not systematically written correctly, though this source of bias should be limited. For example, there were many cases when recorded data for the same patients differed, such as different heights recorded in different parts of the same medical record.

Strengths of the Study

Because the study was based on medical record abstraction, there was no recall bias. To reduce the bias of data abstraction and data entry, data were directly entered in the computer from the medical records. In the electronic abstraction form, all variables were set as required

so that no data were missing. This reduced the amount of missing values and increased the accuracy of data. One additional strength of this retrospective study is that it was relatively inexpensive for investigating these relatively rare diseases.

Conclusion / Recommendation

These findings suggest that improved diabetic control and pre-operative weight reduction may result in a decrease in the incidence of SSI. Outcomes are consistent with the literature. Rates for developing wound infections following CABG are higher in the NMMC than in many hospitals in developed countries, suggesting a need for the adoption of international standards of infectious control.

Further studies with larger samples and follow-up over a longer study period will provide greater statistical power to assess important associations to inform interventions to reduce infection rates. Further recommendations for research based on current study findings include:

- Systematic surveillance for patients having at least one of the independent risk factors, with possible follow up with more aggressive and prophylactic antibiotic treatment,
- Further studies for a longer study period providing greater statistical power to detect associations with rare risk factors and to account for missing dates,
- Further studies to examine potential seasonal/monthly effects on wound infection rates.

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Tables

Table I. *Percent (counts) of patients developing wound infection out of all CABG surgery patients for the years 2006, 2007, 2008 and for the first 3-month of 2009. NMMC Hospital, January 1, 2006 through March 31, 2009.*

	Time periods	2006	2007	2008	*First 3 month of 2009 only*	Total
Infections site	**Chest only**	5.90 (30)	4.70 (24)	3.20 (18)	*5.74 (7)*	**4.64 (79)**
	Leg only	2.36 (12)	2.35 (12)	1.07 (6)	*4.10 (5)*	**2.05 (35)**
	Both	0.39 (2)	0	0.71 (4)	*0.82 (1)*	**0.41 (7)**
	Missing	0.59 (3)	0	0.71(4)	*0*	**0.41 (7)**
Total Infected		**9.25 (47)**	**7.05 (36)**	**5.68 (32)**	***10.65 (13)***	**7.51 (128)**
Total Number of patients		**508**	**511**	**563**	***122***	**1704**

** Dates are for first 3 month of 2009* ***only:*** *from January 1, 2009 through March 31, 2009*

Table II. *Counts and percentages of infected patients for 3-month surgery periods. NMMC Hospital, January 1, 2006 through March 31, 2009.*

		% (n*/N**) of infected among all patients	% (n/N) of infected in sample
3 month time periods	01.01.2006--31.03.2006	7.2 (10/138)	17.5 (10/57)
	01.04.2006--30.06.2006	9.2 (12/131)	16.0 (12/75)
	01.07.2006--30.09.2006	5.9 (5/85)	11.9 (5/42)
	01.10.2006--31.12.2006	13.0 (20/154)	25.6 (20/78)
	01.01.2007--31.03.2007	6.8 (10/146)	13.7 (10/73)
	01.04.2007--30.06.2007	6.5 (9/138)	12.5 (9/72)
	01.07.2007--30.09.2007	10.2 (10/98)	21.7 (10/46)
	01.10.2007--31.12.2007	5.4 (7/129)	12.1 (7/58)
	01.01.2008--31.03.2008	4.9 (6/122)	12.0 (6/50)
	01.04.2008--30.06.2008	6.1 (10/163)	12.1 (10/83)
	01.07.2008--30.09.2008	7.1 (9/126)	16.7 (9/54)
	01.10.2008--31.12.2008	4.6 (7/152)	10.5 (7/67)
	01.01.2009--31.03.2009	10.7 (13/122)	28.3 (13/46)
Total		**7.51 (128/1704)**	**7.5 (128/801)**

** Total number of infected patients in time period*
*** Total number of patients in time period*

Table III. *Number and percentages of pathogens found from infected wounds of 128 patients. NMMC Hospital, January 1, 2006 through March 31, 2009.*

Pathogen	**Leg**	**Chest**	**Both**	**Missing the site**	**Total number**	**%**
Staphylococcus Epidermitis	16	72	6	5	**87**	59,2
Staphylococcus Aureus	17	19	3	1	**34**	23,1
Escherichia coli	16	5	2	0	**19**	12,9
Candida	2	2	1	0	**3**	2,0
Enterococ	0	0	0	1	**1**	0,7
Klebsiella	2	0	0	0	**2**	1,4
Streptococcus pneumonia	1	0	0	0	**1**	0,7
Total	**54**	**98**	**12**	**7**	**147**	**100,0**

Table IV. *Potential dichotomous Risk Factors for developing wound Infection following CABG. NMMC Hospital, January 1, 2006 through March 31, 2009.*

Characteristics and Risk Factors		**Develop Infection**	**Not infected**	**Odds ratio**	**P-value**	**(95% CI)**
Diabetes	*Yes*	61	161	2.93	<0.00005	1.9-4.4
	*No**	65	502			
Gender	*Female*	30	79	2.3	0.0004	1.4-3.8
	*Male**	98	594			
Inotropic Drug Use	*Yes*	23	63	2.39	0.0012	1.3-4.2
	*No**	68	446			
Emergency/urgent	*Yes*	43	247	0.86	0.4681	0.6-1.3
	*No**	82	406			
Cardio pulmonary bypass	*Yes*	83	459	0.86	0.4565	0.6-1.3
	*No**	45	214			
Smoker	*Yes*	46	237	1.13	0.5466	0.7-1.7
	*No**	65	380			
Hypercholesterinemia	*Yes*	35	198	1	0.9860	0.6-1.8
	*No**	27	152			
Gastrointestinal track Diseases	*Yes*	54	293	0.98	0.9314	0.7-1.5
	*No**	66	352			
Respiratory Diseases	*Yes*	14	93	0.80	0.4553	0.4-1.5
	*No**	104	550			
Peripheral Vascular Diseases	*Yes*	16	75	1.23	0.4688	0.6-2.3
	*No**	95	552			
Urinary Track Diseases	*Yes*	25	138	1.08	0.7424	0.6-1.8
	*No**	83	497			

** reference group*

Table V. Potential Continuous Risk Factors for developing wound Infection following CABG. NMMC Hospital, January 1, 2006 through March 31, 2009.

Variable	**Mean ± SD**		**P-value**
	Cases(128)	**Controls(673)**	
Age (in years)	57.2 ± 8.3	56.5 ± 8.6	0.359*
Preoperative Hospital stay days	2.8 ± 5.6	2.8 ± 5.1	0.091
Body mass index, kg/m^2	30.8 ± 4.4	29.0 ± 4.3	<0.001*
Duration of operation, hours	4.6 ±1.1	4.3 ± 1.2	0.001
Artificial breathing time	34.2 ± 60,7	20.6 ± 26.3	0.001
Intubation time	40.7 ± 67.9	23.7 ± 27.6	<0.001
ICU time	89.3 ± 104	62.9 ± 56	0.002
CBP Time	124.6 ±55.3	117.0 ± 45.9	0.477
Clamp time	41.4 ± 27	39.9 ± 21	0.948
blood glucose, mg/dl 0 -24 hours)	8.1 ± 4.5	6.3 ± 2.4	0.001
Albumin	5.7 ± 7.5	4.8 ± 4.4	0.605

* t-*test assuming unequal variances*

Table VI. *Summaries of interaction analysis*

Variable 1	Variable 2		**Odds ratio**	**p-value**	**95% Confidence interval**
Non Smoker	diabetics	No	1.00		
		Yes	2.30	0.002	1.34-3.92
Smoker	diabetics	No	1.00		
		Yes	5.97	<0.0005	3.02-11.82
Duration of operation = T	ICU time = t		1.00		
	ICU time = t+1hour		1.013	0.018	1.005-1.022
Duration of operation = T +1hour	ICU time = t		1.00		
	ICU time = t+1hour		1.011	0.001	1.004-1.018

Table VII*. Multiple logistic regression: First model created using backward elimination method based on p-value*

Factor		Odds ratio	95% confidence interval	p-value
Diabetic	No	1.00		
	Yes	3.01	1.79-5.10	<0.001
Gender	Male	1.00		
	Female	2.24	1.12-4.50	0.023
Smoking	No	1.00		
	Yes	180	1.04-3.12	0.036
Use of inotropic drugs	No	1.00	1.04-3.84	0.039
	Yes	1.99		
BMI(kg/m^2)		1.07	1.01-1.13	0.025
ICU time (hours)		1.002	1.0002-1.006	0.038

Table VIII. *Multiple logistic regression: Second model based on only statistically significant variables, confounders and interactions but without the data having more than 5% missing values*

Factor		Odds ratio	95% confidence interval	p-value
Diabetic	No	1.00		
	Yes	2.44	1.60-3.70	<0.001
Gender	Male	1.00		
	Female	2.08	1.25-3.47	0.005
BMI(kg/m^2)		1.07	1.02-1.12	0.004
Operation time (hours)		1.41	1.13-1.76	0.003
ICU time (hours)		1.01	1.004-1.02	0.002
Operation time*ICU time		0.998	0.9967-0.9997	0.018

Figures

Figure 1

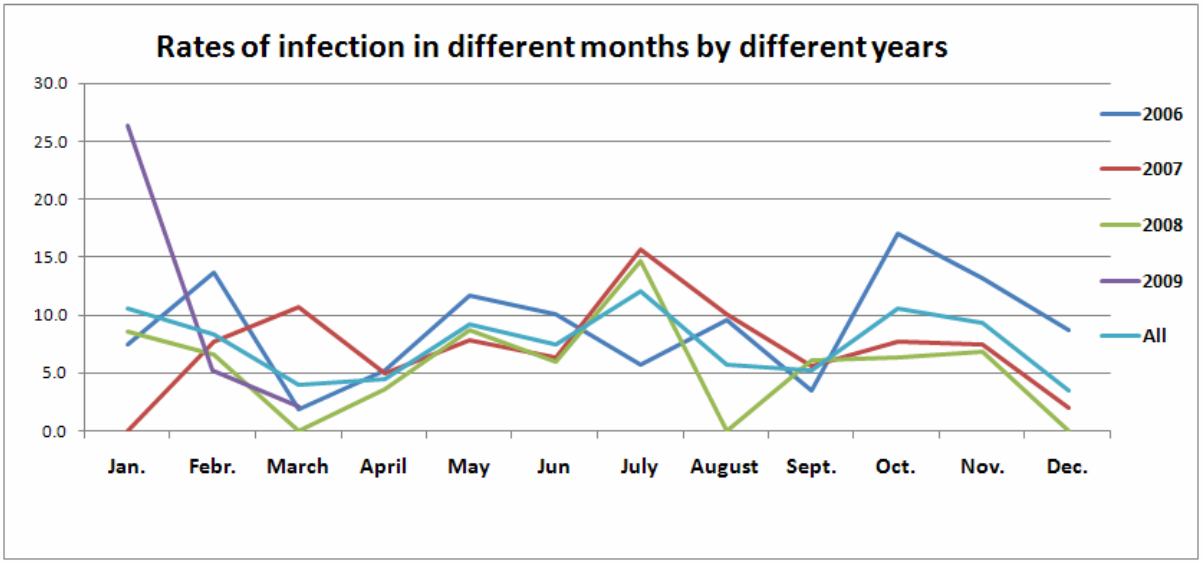


Figure 2 **QQ plot of Age**

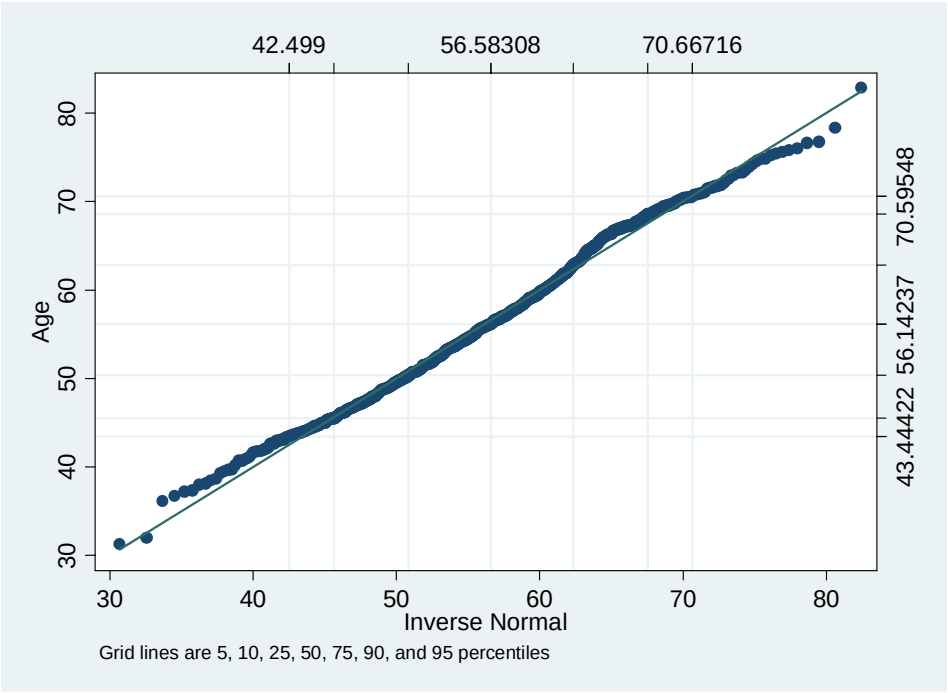
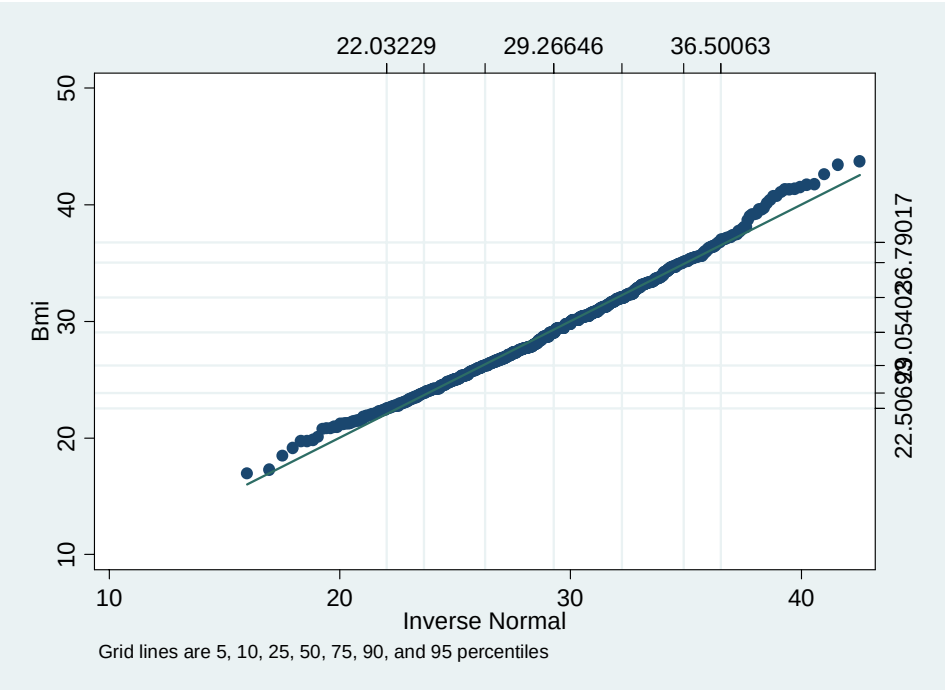
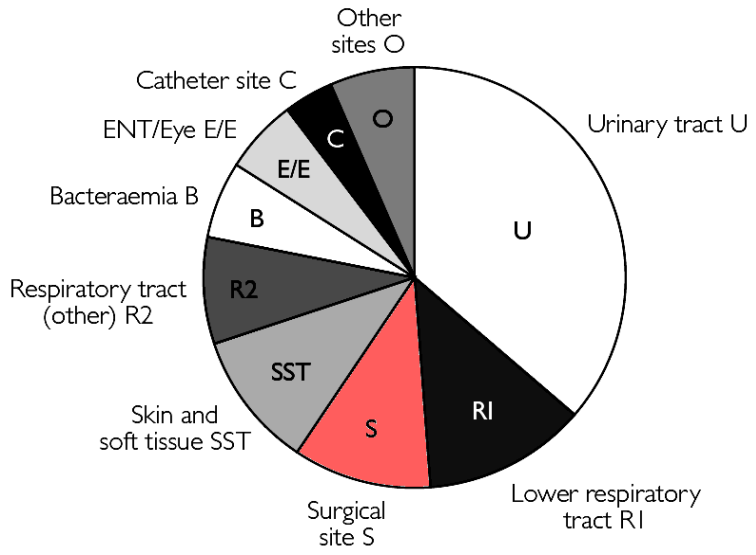


Figure 3 **QQ plot of BMI**

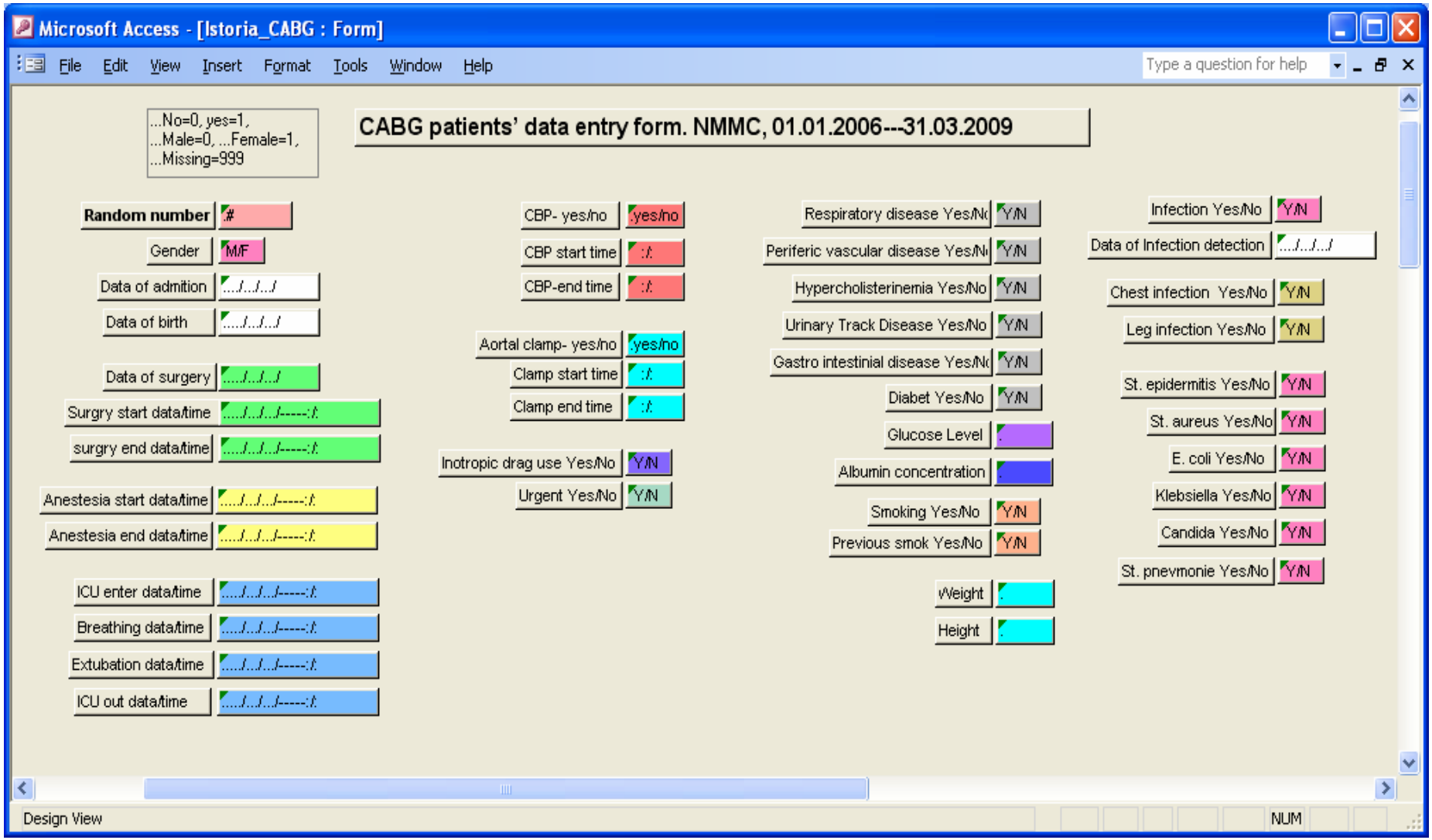


Appendix 1: Sites of the most common nosocomial infections: distribution according to the French national prevalence survey (1996)*



* Adapted fom Enquête nationale de prévalence des infections nosocomiales, 1996. *BEH*, 1997, 36:161–163.

Appendix 2: CABG patients' data entry form



Appendix 3: stata output

1. Gender as a confounder for the relationship between smoking and development of SSI following CABG.

```
. logistic __1INFECTED __2Diabet __7Smok

Logistic regression                               Number of obs   =        728
                                                  LR chi2(2)      =      30.41
                                                  Prob > chi2     =     0.0000
Log likelihood = -295.63266                       Pseudo R2       =     0.0489

------------------------------------------------------------------------------
 __1INFECTED | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   __2Diabet |   3.309672   .7146253     5.54   0.000      2.16767    5.053318
     __7Smok |    1.33859   .2912769     1.34   0.180     .8738287    2.050543
------------------------------------------------------------------------------

. logistic __1INFECTED __2Diabet __7Smok __6Gender

Logistic regression                               Number of obs   =        728
                                                  LR chi2(3)      =      41.16
                                                  Prob > chi2     =     0.0000
Log likelihood =  -290.2596                       Pseudo R2       =     0.0662

------------------------------------------------------------------------------
 __1INFECTED | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   __2Diabet |   3.220659   .7027384     5.36   0.000      2.09998    4.939403
     __7Smok |   1.671888   .3902212     2.20   0.028     1.058122    2.641673
   __6Gender |   2.610418   .7413016     3.38   0.001     1.496192    4.554416
------------------------------------------------------------------------------
```

2. Statistically significant interaction between smoking and diabetes

```
. gen INTdiabSmok= __2Diabet * __7Smok
(73 missing values generated)

. logistic __1INFECTED __2Diabet __7Smok INTdiabSmok

Logistic regression                               Number of obs   =        728
                                                  LR chi2(3)      =      35.08
                                                  Prob > chi2     =     0.0000
Log likelihood = -293.29575                       Pseudo R2       =     0.0564

------------------------------------------------------------------------------
 __1INFECTED | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   __2Diabet |   2.296296   .6272107     3.04   0.002     1.344407    3.922159
     __7Smok |   .9064039   .2587502    -0.34   0.731     .5180005    1.586037
 INTdiabSmok |   2.600095   1.150817     2.16   0.031      1.09205    6.190645
------------------------------------------------------------------------------

.
. lincom  __2Diabet+ INTdiabSmok

 ( 1)  __2Diabet + INTdiabSmok = 0

------------------------------------------------------------------------------
 __1INFECTED | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   5.970588   2.079397     5.13   0.000     3.016937    11.81593
------------------------------------------------------------------------------

.
```

3. Statistically significant interaction between duration of operation and ICU time.

```
. gen INToperICU=__12OperationTime*__15ICUtime
(45 missing values generated)

. logistic __1INFECTED __15ICUtime __12OperationTime INToperICU

Logistic regression                                 Number of obs   =        756
                                                    LR chi2(3)      =      24.68
                                                    Prob > chi2     =     0.0000
Log likelihood = -321.77059                         Pseudo R2       =     0.0369

------------------------------------------------------------------------------
 __1INFECTED | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 __15ICUtime |   1.014044   .0044378     3.19   0.001     1.005383    1.022779
__12Operat~e |   1.456988   .1583311     3.46   0.001     1.177486    1.802836
  INToperICU |   .9980717   .0007874    -2.45   0.014     .9965296    .9996162
------------------------------------------------------------------------------

. lincom __15ICUtime+ INToperICU

 ( 1)  __15ICUtime + INToperICU = 0

------------------------------------------------------------------------------
 __1INFECTED | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.012089   .0036758     3.31   0.001      1.00491    1.019319
------------------------------------------------------------------------------
```

4. Correlation analysis between duration of artificial breathing and intubation time

```
. correlat __13Intubationtime __14Artifitialbreathingtime
(obs=763)

             | __13In~e __14Ar~e
-------------+------------------
__13Intuba~e |   1.0000
__14Artifi~e |   0.9647   1.0000
```

5. First model created using backward elimination method based on p-value

```
    . logistic __1INFECTED  __2Diabet __6Gender __7Smok __11BMI __15ICUtime
__20USEofInotropiki

    Logistic regression                             Number of obs   =        524
                                                    LR chi2(6)      =      47.79
                                                    Prob > chi2     =     0.0000
    Log likelihood = -196.55968                     Pseudo R2       =     0.1084

    ------------------------------------------------------------------------------
     __1INFECTED | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
    -------------+----------------------------------------------------------------
       __2Diabet |   3.018491   .8064009     4.14   0.000     1.788086    5.095555
       __6Gender |   2.244669   .7958915     2.28   0.023      1.12032     4.49741
         __7Smok |   1.799829   .5056828     2.09   0.036     1.037711    3.121664
         __11BMI |   1.066835   .0307742     2.24   0.025     1.008192    1.128889
    __15ICUtime |    1.00292   .0014114     2.07   0.038     1.000158     1.00569
    __20USEofI~i |    1.99492   .6663932     2.07   0.039      1.03654    3.839416
------------------------------------------------------------------------------
```

6. Second model based on only statistically significant variables, confounders and interactions but without the data that have missing values more than 5%

```
. logistic __1INFECTED  __2Diabet __6Gender __11BMI __12OperationTime __15ICUtime INToperICU

Logistic regression                               Number of obs   =        749
                                                  LR chi2(6)      =      66.00
                                                  Prob > chi2     =     0.0000
Log likelihood = -298.23193                       Pseudo R2       =     0.0996

------------------------------------------------------------------------------
 __1INFECTED | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   __2Diabet |   2.435208   .5187752     4.18   0.000     1.603997    3.697162
   __6Gender |   2.080434   .5436038     2.80   0.005     1.246638    3.471901
     __11BMI |   1.072166    .025655     2.91   0.004     1.023045    1.123647
__12Operat~e |    1.40832   .1603496     3.01   0.003     1.126638    1.760427
 __15ICUtime |   1.013118   .0042916     3.08   0.002     1.004741    1.021564
  INToperICU |   .9982045   .0007607    -2.36   0.018     .9967147    .9996965
------------------------------------------------------------------------------



. lfit,group(10)

Logistic model for __1INFECTED, goodness-of-fit test

  (Table collapsed on quantiles of estimated probabilities)

       number of observations =       749
             number of groups =        10
      Hosmer-Lemeshow chi2(8) =         9.70
                  Prob > chi2 =         0.2866
```

Interaction found in this model

```
. lincom __15ICUtime+  INTOPtimICU

 ( 1)  __15ICUtime + INTOPtimICU = 0

------------------------------------------------------------------------------
 __1INFECTED | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.011299   .0035613     3.19   0.001     1.004343    1.018303
------------------------------------------------------------------------------
```

7. Third model adjusted for months based on only statistically significant variables, confounders and interactions but without the data that have missing values more than 5%

```
. xi:logistic __1INFECTED  __2Diabet __6Gender __11BMI __12OperationTime __15ICUtime
INToperICU i.Month
i.Month           _IMonth_1-12        (naturally coded; _IMonth_1 omitted)

Logistic regression                               Number of obs   =        749
                                                  LR chi2(17)     =      81.86
                                                  Prob > chi2     =     0.0000
Log likelihood = -290.29715                       Pseudo R2       =     0.1236

------------------------------------------------------------------------------
 __1INFECTED | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   __2Diabet |   2.545003   .5587983     4.25   0.000      1.65498    3.913668
   __6Gender |   2.170668   .5825404     2.89   0.004     1.282794    3.673074
     __11BMI |   1.076331   .0262316     3.02   0.003     1.026127    1.128992
__12Operat~e |   1.383295    .163078     2.75   0.006     1.097907    1.742865
 __15ICUtime |   1.013545    .004552     3.00   0.003     1.004662    1.022506
  INToperICU |   .9981781   .0007772    -2.34   0.019      .996656    .9997025
   _IMonth_2 |   .8701041   .3886671    -0.31   0.755     .3625332    2.088309
   _IMonth_3 |   .5496026   .2949892    -1.12   0.265     .1919472    1.573677
   _IMonth_4 |   .3767751   .2209906    -1.66   0.096     .1193508     1.18943
   _IMonth_5 |   .6542578   .3010229    -0.92   0.356     .2655293    1.612075
   _IMonth_6 |    .684147   .3315365    -0.78   0.433     .2646419    1.768643
   _IMonth_7 |   1.210088   .5987422     0.39   0.700     .4588268    3.191427
   _IMonth_8 |   .7400229   .4601879    -0.48   0.628     .2187359    2.503631
   _IMonth_9 |    .535711   .2998953    -1.11   0.265     .1788221    1.604871
  _IMonth_10 |   1.303495   .6110546     0.57   0.572     .5200936    3.266909
  _IMonth_11 |   1.086713   .5066508     0.18   0.858     .4357776    2.709972
  _IMonth_12 |    .266626   .1587238    -2.22   0.026     .0830191    .8563021
------------------------------------------------------------------------------

. lfit,group(10)

Logistic model for __1INFECTED, goodness-of-fit test

  (Table collapsed on quantiles of estimated probabilities)

      number of observations =       749
            number of groups =        10
     Hosmer-Lemeshow chi2(8) =        12.39
                 Prob > chi2 =         0.1346
```

8. Fourth model adjusted for 3-month time periods based on only statistically significant variables, confounders and interactions but without the data that have missing values more than 5%

```
. xi:logistic __1INFECTED  __2Diabet __6Gender __11BMI __12OperationTime __15ICUtime
INToperICU i.TimeDist3
i.TimeDist3       _ITimeDist3_1-13    (naturally coded; _ITimeDist3_1 omitted)

Logistic regression                               Number of obs   =        749
                                                  LR chi2(18)     =      97.53
                                                  Prob > chi2     =     0.0000
Log likelihood = -282.46589                       Pseudo R2       =     0.1472

------------------------------------------------------------------------------
 __1INFECTED | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   __2Diabet |   2.731031   .6084388     4.51   0.000     1.764777    4.226331
   __6Gender |   2.092192   .5771792     2.68   0.007     1.218367    3.592734
     __11BMI |   1.085451   .0272357     3.27   0.001     1.033361    1.140166
__12Operat~e |    1.42651   .1730142     2.93   0.003     1.124701    1.809309
 __15ICUtime |   1.014632   .0045304     3.25   0.001     1.005792    1.023551
  INToperICU |    .997958   .0008377    -2.44   0.015     .9963176    .9996012
_ITimeDis~_2 |   1.204778   .6106499     0.37   0.713     .4461389    3.253451
_ITimeDis~_3 |   .5127558   .3265317    -1.05   0.294     .1471807    1.786366
_ITimeDist~4 |   2.026735   .9572883     1.50   0.135     .8030615    5.114995
_ITimeDist~5 |   .7470691   .3913886    -0.56   0.578     .2675576    2.085952
_ITimeDist~6 |   .5681533   .3038487    -1.06   0.290     .1991785    1.620648
_ITimeDist~7 |   1.333877   .7459981     0.52   0.606     .4457221     3.99179
_ITimeDist~8 |   .3830498   .2440289    -1.51   0.132      .109896    1.335146
_ITimeDist~9 |   .4512366   .2756342    -1.30   0.193     .1362871    1.494011
_ITimeDis~10 |    .489895   .2682524    -1.30   0.193     .1674979    1.432836
_ITimeDis~11 |   1.206156   .6666152     0.34   0.735     .4082848    3.563226
_ITimeDis~12 |   .5959881   .3364473    -0.92   0.359     .1971139    1.802013
_ITimeDis~13 |   3.652392   2.131437     2.22   0.026     1.163695    11.46346
------------------------------------------------------------------------------

.

. lfit,group(10)

Logistic model for __1INFECTED, goodness-of-fit test

  (Table collapsed on quantiles of estimated probabilities)

      number of observations =       749
            number of groups =        10
     Hosmer-Lemeshow chi2(8) =         9.70
                Prob > chi2 =         0.2866

.
```