FULL LENGTH ARTICLE

# Impact of blood transfusion on major infection after isolated coronary artery bypass surgery: Incidence and risk factors

Shaikhah Awadh Al-Harbi [a,b], Norah Alkhayal [a,b], Afrah Alsehali [a,b], Shatha Alshaya [a,b], Wesam bin Obaid [a,b], Alaa Althubaiti [b,c], R.E. van Onselen [b,d], Mohmed Al Annany [d,e], Ahmed A. Arifi [b,d,*]

[a] College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh
[b] King Abdullah International Medical Research Center, Riyadh
[c] Department of Basic Medical Sciences, College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh
[d] Cardiac Clinical Research, Cardiac Surgery, Cardiac Sciences, King Abdulaziz Cardiac Center, Ministry of National Guard, Riyadh
[e] Ain Shams University Cario, Egypt

[a,b,c,d,e] Saudi Arabia

*Background/aim:* **Cardiac surgery is considered one of the conditions that require a transfusion of blood and blood products in large amount. Infections are one of the most common complications after cardiac surgery. The aim of this study is to assess the impact of blood transfusion on major infections after isolated coronary artery bypass surgery (CABG).**

*Methods:* **A retrospective cohort study was conducted at King Abdulaziz Cardiac Center. Eligible adult patients, aged >18 years, who underwent an isolated CABG from 2015 to 2016, were included. Patient demographic information, as well as pre-, intra-, and postoperative data were collected from the electronic hospital information system charts and perfusion records. For data analysis, categorical pre- and postoperative variables were summarized by frequencies and percentages, whereas for continuous variables, means and standard deviation or median and interquartile ranges were used.**

*Results:* **The sample size was 459 patients. Red blood cells (RBCs) were transfused in 60.1% of the patients, and the median number of units transfused per patient was 2. The mean hemoglobin threshold for transfusion was 8.2 (standard deviation þ 3.6) g/dL. The mean EuroSCORE of RBC recipients was 3.8 þ 5.9% and that of non-RBC recipients was 2.0 þ 2.0%. In both groups (RBC recipients and non-RBC recipients), the most frequent infections after CABG were pneumonia (12% and 8.7%, respectively), deep surgical site infection (3.6% and 0.5%, respectively), and superficial sternal infection (6.9% and 3.8%, respectively), with a statistically significant difference (all $p < 0.05$). Patients receiving a blood transfusion at any stage during the intraoperative or postoperative period were 2.6 times more likely to develop an infection compared with those who did not receive a blood transfusion. The recipients of a blood transfusion experienced a longer hospital stay compared with the non-recipients at 11.5 þ 9.8 days versus 8.7 þ 3.4 days, respectively.**

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* Corresponding author at: Cardiac Clinical Research, Cardiac Surgery, Cardiac Sciences, King Abdulaziz Cardiac Center, Ministry of National Guard, P.O. Box 22490, Riyadh 11426, Saudi Arabia.
E-mail address: arifiahmed@hotmail.com (A.A. Arifi).

P.O. Box 2925 Riyadh – 11461KSA
Tel: +966 1 2520088 ext 40151
Fax: +966 1 2520718
Email: sha@sha.org.sa
URL: www.sha.org.sa

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*Conclusions:* **Blood transfusion appears to increase the risk of infection post-CABG. However, increased understanding of the role of other potential clinical confounding variables that may impact the infection rate is required. We recommend management strategies that limit RBC transfusion.**

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*Keywords:* Blood transfusion, Cardiac surgery, Infection, Surgical site infection

## 1. Introduction

One of the most common healthcare-associated infections among patients undergoing cardiac surgery is surgical site infection (SSI) [1]. SSI is defined as an infection connected to the surgical cut occurring within 30 days postoperatively or within 90 days if a prosthetic material has been implanted during surgery [1]. SSI accounts for more than 25% of all healthcare-associated infections in surgical patients. Intensive care unit (ICU) admissions, readmissions, prolonged complications, and mortality are frequent complications of SSIs. According to the Centers for Disease Control (CDC), SSI is classified as superficial (involving skin and subcutaneous tissue) or complex (involving deep soft tissue and organ spaces) [1]. Regarding the general pathophysiology of SSIs, studies hypothesized that they occur as a result of pathogens gaining access to surgical wounds either by direct inoculation from local factors such as normal flora of the skin or contaminated drains or seeding of pathogens from a distant site by blood [2].

Risk factors for SSI are patient- and surgery-related. Important patient-related factors include older age, obesity, smoking, and comorbidities such as diabetes mellitus (DM), impaired immunity, and blood transfusion. Surgical risk factors include prolonged procedure time and inadequacies in either the surgical scrubbing procedure or the antiseptic preparation of the skin. The consequences of SSIs are not restricted to morbidity, but are also a significant financial burden on the healthcare system because of longer hospitalization leading to increased cost [3,4].

Among other factors, blood transfusion plays a major role in the development of postoperative infections, including SSIs following cardiac surgery, because of the frequency of perioperative blood transfusions during cardiac surgery [5,6]. Moreover, blood transfusion has several side effects such as organ dysfunction, mortality, and an immunosuppressive effect that could cause infectious complications if the quantity of transfused blood products exceeds a certain threshold [7,8].

**Abbreviations**

| | |
|---|---|
| SSI | Surgical site infection |
| CDC | Centers for Disease Control |
| NGHA | National Guard Health Affairs |
| CABG | Coronary artery bypass grafting surgery |
| RBC | Red blood cell |
| ASA | American Society of Anesthesiology |

The exact role of blood transfusions in the pathogenesis of SSIs after cardiac surgery, whether as a direct immunosuppressant or storage marker for morbidity, remains unclear [5,7,8]. Hence, the contribution of the study is to reduce future SSIs by investigating the impact of blood transfusions. To the best of our knowledge, the topic is under-researched especially in the Kingdom of Saudi Arabia. In our study, we aimed to investigate the association of perioperative blood transfusions and the development of SSIs in a cohort of cardiac surgery patients at King Abdulaziz Cardiac Center, King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia.

## 2. Materials and methods

A retrospective cohort study has been conducted on 459 consecutive patients who underwent CABG surgery in the Department of Cardiac Surgery, King Abdulaziz Cardiac Center, King Abdulaziz Medical City, Riyadh, Saudi Arabia, from January 2015 until December 2016. Eligible patients were adults aged >18 years who underwent isolated CABG. The study was approved by the Institutional Review Board of the health institution. Patients without SSIs were compared with patients with postoperative SSIs. We assessed the independent impact of perioperative blood and blood product transfusion on major infection within 30 days of surgery. Wound

infections were detected according to the CDC classification of SSI as shown in Appendix 1 [1]. The data were collected from the electronic hospital information system charts and perfusion records, and they reviewed by the research associate and practitioners for accuracy.

Data were divided into pre-, intra-, and postoperative variables. Preoperative variables included patient demographics [age, body mass index (BMI), and sex], comorbidities, or other risk factors (DM, chronic obstructive pulmonary diseases, creatinine level, American Society of Anesthesiology score, tobacco use, and EuroSCORE), which are used as a model for prediction of mortality after cardiac surgery (Table 1). Procedural details included surgery status, reoperation, preoperative length of stay (LOS), number of bypass grafts, duration of extracorporeal bypass, duration of surgery, type of skin preparatory agent, antibiotic administration, lowest hemoglobin level intraoperative, as well as type and number of blood products used. Postoperative variables included the LOS, reoperation, type and number of blood products used, and major infections including SSI, deep incisional SSI occurring at the primary incision site or at the secondary incision site (e.g., saphenous harvest site, groin cannulation site), mediastinitis, and pneumonia.

Data were analyzed using the SPSS database (IBM SPSS Statistics; SPSS Inc., Chicago, IL, USA) and GraphPad Quick Cals. We reported frequencies and percentages for categorical variables and mean, standard deviation (SD), and the median for continuous variables. A multiple logistic regression model was used to determine the relationship between blood transfusion with the risk of infection as the dependent variable. Age, sex, smoking status, preoperative creatinine level, diabetes status, smoking status, asthma status, and the total number of blood units intra- and postoperatively were included as independent variables. The association between variables and the outcomes was tested by a Chi-square test, and the R-squared is reported for SSI risk factors. A $p$ value of <0.05 was considered statistically significant.

## 3. Results

A total of 459 patients were retrospectively enrolled in the study, of which 276 (60.1%) were assigned to the RBC group and 183 (39.9%) to the No RBC group. The baseline characteristics are shown in Table 1. The mean age patients in the No RBC group was 60.6 ± 10.1 years, which is not significantly higher than that in the RBC group. The mean EuroSCORE II was found to be significantly ($p < 0.001$) higher in the RBC group compared with the No RBC group at 3.8 ± 5.9% and 2.01 ± 2.0%, respectively. In the current study, the most common infection after CABG was pneumonia (10.7%). Patients in the RBC group had significantly higher ($p < 0.05$) incidence of deep sternal infection, superficial sternal infection, and pneumonia (3.6% vs. 0.5%, 6.9% vs. 3.8%, and 12% vs. 8.7%, respectively). There was no statistically significant difference between the two groups in terms of leg infection or urinary tract infections ($p > 0.05$ in both cases) (Table 2). In terms of sex, females had almost three times higher risk of developing an SSI compared with males [odds ratio (OR) = 2.9; 95% confidence interval (CI), 1.2–6.7; $p < 0.05$)]. Notably, each unit of blood given postoperatively increased the risk of infection by 20% (OR = 1.2; 95% CI, 1.1–1.4; $p < 0.001$). The median number of units transfused per patient was 2 [interquartile range (IQR) = 2–5]. The mean hemoglobin threshold for transfusion was 8.2 (SD ± 3.6) g/dL. Patients receiving a blood transfusion at any stage during the intra- or postoperative period were 2.6 times more likely to have infection compared with those who did not receive any blood transfusion (Table 3). Furthermore, the recipients of a blood transfusion experienced a longer preoperative and postoperative hospital stay in comparison with those in the No RBC group (Table 4).

*Table 1. Baseline characteristics of the studied participants.*

| Patient characteristics | Overall ($n$ = 459 | RBC ($n$ = 276) | No RBC ($n$ = 183) | $p$ |
|---|---|---|---|---|
| Age, mean ± SD | 60.6 ± 10.1 | 62.0 ± 10.0 | 58.5 ± 10.1 | 0.3[a] |
| Female, $n$ (%) | 66 (14.4) | 17 (6.1%) | 49 (26.7%) | <0.0001[b] |
| Diabetes mellitus, $n$ (%) | 345 (75.2%) | 203 (73.6%) | 143 (77.6%) | 0.14[b] |
| COPD, $n$ (%) | 8 (1.7%) | 3 (1.0%) | 5(2.7%) | 0.4[b] |
| Asthma, $n$ (%) | 14 (3.1%) | 11(4.0%) | 3 (1.6%) | 1.0[b] |
| Current smoker, $n$ (%) | 87 (19%) | 41(14.9%) | 46 (25.1%) | 0.0140[b] |
| EuroSCORE II %, mean ± SD | 3.1 ± 4.8% | 3.8 ± 5.9% | 2.0 ± 2.0% | <0.0001[a] |

COPD = chronic obstructive airways disease; RBC = red blood cell; SD = standard deviation.
[a] Based on Wilcoxon's rank test.
[b] Based on chi-square test or Fisher's exact test.

*Table 2. Infections in overall, no RBC, and RBC groups.*

| Variable | Overall ($n$ = 459) | RBC ($n$ = 276) | No RBC ($n$ = 183) | $p$ |
|---|---|---|---|---|
| Deep sternal, $n$ (%) | 11 (2.4%) | 10 (3.6%) | 1(0.5%) | 0.006 |
| Superficial sternal infection, $n$ (%) | 26 (5.7 %) | 19 (6.9%) | 7(3.8%) | 0.018 |
| Leg infection, $n$ (%) | 9 (2.0%) | 5 (1.8%) | 4(2.2%) | 0.4 |
| Pneumonia, $n$ (%) | 49(10.7%) | 33(12%) | 16 (8.7%) | 0.004 |
| UTI, $n$ (%) | 21(4.6%) | 16(5.8%) | 5 (2.7%) | 0.1 |
| Septicemia, $n$ (%) | 6 (1.3%) | 4 (1.4%) | 2(1.1%) | 0.8 |

RBC = red blood cell; UTI = urinary tract infection.

*Table 3. The adjusted risk of infection by sex, and post- and intraoperative blood units.*

| Variable | Odds ratio | LCL | UCL | $p$[a] |
|---|---|---|---|---|
| Female vs. male | 2.9 | 1.2 | 6.7 | 0.014 |
| Postoperative blood units | 1.2 | 1.1 | 1.4 | 0.005 |
| Intraoperative blood units | 0.983 | 0.8 | 0.8 | 0.9 |

LCL = upper control limit; UCL = lower control limit.
[a] Based on multiple logistic regression modeling the risk of infection.

## 4. Discussion

The finding that an association may exist between blood transfusion and an increased SSI risk in CABG patients was not surprising, as multiple studies have shown a relationship between perioperative blood transfusion and postoperative infection risk. The association between SSI and blood transfusion, however, is underresearched compared to other more established SSI risk factors, because the role of blood transfusion in the pathogenesis of postoperative infections is controversial and has been debated for more than three decades. The current study revealed that blood transfusion, particularly postoperative transfusion, was strongly associated with major postoperative infections in a dose-related fashion, specifically between RBC transfusion and developing pneumonia. A study conducted by Horvath et al. [9] provides support for the current study. In their observational study of postoperative infections among adults undergoing cardiac surgery at 10 centers in the United States and Canada in 2013, the authors report that each RBC unit transfused was associated with a 29% increase in the crude risk of a major infection. In addition, for RBC recipients, the most common infection was pneumonia at 3.6%, compared to 12% in the current study. Another study conducted by Mohnle et al. [10] in 2011, which investigated coronary artery bypass patients enrolled in a multicenter study of perioperative ischemia, reported that transfused patients were more likely to have postoperative cardiac events and harvest site infection. Moreover, multiple randomized controlled trials and many observational studies [11–15] have described the potential association between blood transfusion and an increased postoperative SSI risk. Such an association has been reported in a variety of surgical procedures including CABG surgery [16,17].

By contrast, several studies reported an opposing view. Ali et al. [18] did not find such an association and suggested that ‘‘clinicians should reconsider withholding blood transfusion in patients solely because of concerns of predisposition to infection.’’ Similarly, in their review of the reported evidence up to 1994, Vamvakas and Moore [12] concluded that a causal pathway was not established and there were many confounders that could render transfusion only a surrogate marker for infection and other adverse outcomes. A third study performed by Talbot et al. [19], who investigated the potential risk of blood transfusion in the development of SSI, concluded that the role of transfusion as an immunosuppressant or as a clear marker for SSI and morbidity remained unclear.

In addition to increasing the risk of SSI, our results indicated that blood transfusion increases the length of hospital stay (LOS). In a systematic review of mediastinitis and blood transfusion in cardiac surgery, the authors suggested that blood transfusions are associated with an increased risk

*Table 4. Length of hospital stay according to red blood cells (RBCs) transfused and nontransfused patients.*

| | All RBC transfused (intra-/postoperative) cohort ($n$ = 276) | No RBC transfused cohort ($n$ = 183) |
|---|---|---|
| Preoperative mean | 151.5 h, 6.3 ± 4.5 d | 143.8 h, 6.0 ± 4.9 d |
| Postoperative mean | 276.5 h, 11.5 ± 9.8 d | 208.5 h, 8.7 ± 3.4 d |

of developing SSI and that an individual risk and benefit assessment should to be done prior to transfusion to avoid increased LOS as a result of SSI [8]. Galas et al. [20] reported that RBC transfusion is an independent risk factor for increased LOS in patients undergoing cardiac surgery, which highlights the adequacy of restrictive transfusion therapy in patients undergoing cardiac surgery. Female patients as well as patients with a higher EuroSCORE are more likely to receive RBC transfusion, which emphasizes the need to maximize efforts to improve perioperative care to prevent RBC transfusion related adverse events, including increased LOS [20].

In a large retrospective analysis of patients who underwent isolated CABG surgery, it was found that RBC transfusion is associated with a dose-dependent increased risk of postoperative cardiac complications, serious infection, neurologic complications, renal failure, overall morbidity, and in-hospital mortality [21]. Similarly, in a retrospective study, Murphy et al. [22] showed that RBC transfusion is strongly associated with infection, hospital stay, increased early and late mortality, and hospital costs.

In agreement with our results, an analysis of 438,050 surgical procedures from the German National Nosocomial Infections Surveillance System to assess Gender-Specific Differences in Surgical Site Infections found that women had a higher risk for SSI in cardiac surgery [23]. In addition, previous studies reported that female sex is among the risk factors for leg harvest site infection after CABG surgery [24–26]. The effect of RBC transfusion on bacterial infections after cardiac operations has been assessed previously, and sternal wound infection was reported in both retrospective and prospective studies [27,28]. These findings are in line with the current study. Olsen et al. [25] showed that postoperative transfusion of 5 or more units of RBC is a risk factor for leg harvest SSI after CABG surgery. In the current study, blood transfusion showed a higher but nonsignificant increase in the risk of a leg infection. The difference in the findings may be attributable to the median number of units transfused per patient in our study, which was 2 [interquartile range (IQR) = 2–5].

### *4.1. Study limitation*

The study has several limitations that should be taken under consideration. It was not determined if the blood was allogeneic or autologous, or whether it was leucocyte depleted, which may have an impact on the potential immunosuppressive effects of the transfusion.

## 5. Conclusion

In conclusion, the study showed an association between blood transfusion and SSI and other infectious complications post cardiac surgery. Patients receiving a blood transfusion at any stage during the intraoperative or postoperative period are 2.6 times more likely to have infection compared with those who did not receive any transfusion. Each unit of blood given postoperatively increased the risk of infection by 20%. Every effort should be taken to adopt the blood conservation concept.

## Conflicts of interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

## Appendix 1

### *Infection definitions*[a]

**Deep incisional surgical site infection, primary (DIP)**

A surgical site infection (SSI) that is identified in the primary chest incision and meets all of the following criteria:

(1) Infection occurs within 30 days after the operative intervention.
(2) Infection involves deep soft tissues (e.g., fascial and muscle layers).
(3) Patient has at least one of the following:
   a. Purulent discharge from the deep incision, but not from the organ/space component of the surgical site;
   b. A deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture positive, or not cultured[b] when the patient has at least one of the following: fever 38 °C, localized pain, or tenderness;
   c. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination;
   d. Diagnosis of deep incisional SSI by the surgeon or attending physician.

**Deep incisional surgical site infection, secondary (DIS)**

An SSI that is identified in the secondary incision [e.g., donor site (leg) incision for coronary artery bypass surgery (CABG)] in a patient who has had an operation with one or more incisions and meets all of the following criteria:

(1) Infection occurs within 30 days after the operative intervention.
(2) Infection involves deep soft tissues (e.g., fascial and muscle layers).
(3) Patient has at least one of the following:
   a. Purulent discharge from the deep incision, but not from the organ/space component of the surgical site;
   b. A deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture positive, or not cultured[b] when the patient has at least one of the following: fever 38 °C, localized pain or tenderness;
   c. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination;
   d. Diagnosis of deep incisional SSI by the surgeon or attending physician.

**Mediastinitis (MED)**

Mediastinitis must meet at least one of the following criteria:

(1) Patient has organisms cultured from mediastinal tissue or fluid obtained during a surgical operation or needle aspiration.
(2) Patient has evidence of mediastinitis seen during a surgical operation or histopathologic examination.
(3) Patient has at least one of the following signs or symptoms with no other recognized cause: fever 38 °C, chest pain, or sternal instability, and at least one of the following:
   a. Purulent discharge from mediastinal area;
   b. Organisms cultured from blood or discharge from mediastinal area.

**Pneumonia (PNEU)**

Clinically defined pneumonia must meet all of the following criteria:

(1) At least one or more chest radiographs no earlier than 2 days after surgery, with at least one of the following:
   a. New or progressive and persistent infiltrate;
   b. Consolidation;
   c. Cavitation.
(2) Patient has at least one of the following signs or symptoms: fever 38 °C with no other recognized cause, leukopenia (4000 WBC/$mm^3$) or leukocytosis (12,000 WBC/$mm^3$), or altered mental status with no other recognized cause (for patients who are 70 years old), and at least two of the following:
   a. New onset of purulent sputum, change in character of sputum, increased respiratory secretions, or increased suctioning requirements;
   b. New onset or worsening cough, dyspnea, tachypnea;
   c. Rales or bronchial breath sounds;
   d. Worsening gas exchange (e.g., $O_2$ desaturations, increased oxygen requirements, increased ventilator demand).

[a]Most infection definitions have been adapted from the CDC (available at: www.cdc.gov).

[b]A culture-negative finding does not meet this criterion.

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