Impact of an Unknown HIV Serostatus on the Risk of Postoperative Cardiovascular Morbidity and Mortality

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Abstract

Background: The impact of an unknown human immunodeficiency virus (HIV) serostatus on postoperative outcomes, such as major adverse cardiovascular events (MACE), in surgical settings with a high prevalence of HIV infection has not yet been established. This was the impetus for the current study.

Methods: This was an unmatched case-control study of 460 patients who underwent vascular/general surgery at a tertiary South African hospital (patients with MACE/cases = 92 and patients without MACE/controls = 368). Data related to age, gender, and the presence of established cardiovascular risk factors in surgical settings were extracted from patient medical records. HIV serostatus for each patient was recorded as positive or negative (where preoperative documentation of such test results existed) or unknown (where no preoperative documentation of an HIV test result existed). Data were analyzed in accordance with recommendations for unmatched case-control study designs.

Results: Adjusted analysis revealed that there was no difference in the risk of postoperative MACE between HIV-negative (reference group), HIV-positive (odds ratio: 1.16, 95% confidence interval: 0.42-3.21) and HIV-unknown serostatus (odds ratio: 0.85, 95% confidence interval: 0.47-1.54) groups.

Conclusion: Our study findings suggest that an unknown HIV serostatus is not a risk factor for postoperative MACE. HIV serostatus should not be included in cardiovascular risk stratification methods in surgical settings with a high prevalence of HIV.

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Introduction

Globally, over 30 million people are infected with human immunodeficiency virus (HIV).[1] In South Africa, 11-20% of the population is thought to be infected with HIV.[2] However, there appears to be suboptimal uptake of HIV counseling and testing in the South African adult population, with almost half of adult patients not knowing their HIV serostatus.[2] The large proportion of the South African adult population with an unknown HIV status is alarming. Findings from a recent study of medically-treated (non-surgical) patients attending a South African hospital located in a region of the country with a high prevalence of HIV infection suggest that an unknown HIV serostatus might potentially be associated with undesirable patient outcomes.[3] Determining HIV serostatus is important in high prevalence settings as this facilitates identification of patients with previously undiagnosed HIV infection, thereby allowing for the initiation of antiretroviral therapy and effective disease management in these patients.[4] An increasing burden of infectious, non-communicable disease with high levels of injury and trauma has resulted in a growing South African population requiring surgical intervention and treatment requiring surgical intervention for the treatment of these conditions at some point during their lifetime.[5] Many of these patients are at risk of developing complications following their surgery, with major adverse cardiovascular events being amongst the most important complications during the postoperative period.[6] A study by Redman et al. found the incidence of postoperative cardiovascular morbidity and mortality to be similar in South African vascular surgery patients with or without HIV infection.[7] Many patients in that study did not consent to HIV counseling and testing, so the unknown HIV serostatus group was not included in the final data analysis.[7] Surgical patients who are known to be HIV-positive prior to their surgery are initiated on antiretroviral therapy. Patients with unknown HIV serostatus, particularly in HIV-endemic settings, are potential undiagnosed HIV-positives. However, as antiretroviral therapy is only provided to those patients who are diagnosed HIV-positive, undiagnosed HIV-positives go untreated. HIV-positive surgical patients who receive antiretroviral therapy are at a lower risk of perioperative mortality when compared with HIV-positive surgical patients who do not receive antiretroviral therapy.[8] As there is cardiovascular involvement in a large proportion of deaths following non-cardiac surgery,

it is possible that antiretroviral therapy reduces the risk of perioperative cardiovascular complications in HIV-positive surgical patients. This possibility is somewhat supported by Redman et al., who reported a lower incidence of perioperative cardiovascular morbidity and mortality in HIV-positive vascular surgery patients who received antiretroviral therapy versus an antiretroviral therapy naïve vascular surgery patient group (9% versus 18%).[7] It would appear that universal testing of surgical patients for HIV in high-prevalence settings, and initiating those who test positive on antiretroviral therapy, could potentially reduce perioperative cardiovascular morbidity and mortality in this patient population. However, the rollout of universal HIV testing for all surgical patients in resource-constrained settings can only be considered once a direct link between an unknown HIV serostatus and postoperative cardiovascular morbidity and mortality is established. Therefore, this study sought to determine the impact of an unknown HIV serostatus on postoperative major adverse cardiovascular events (MACE) in a setting with a high prevalence of HIV infection.

Methods

Study design, setting, and study population: This was an unmatched case-control study of adult (aged 18 years old or older) South African patients who underwent vascular or general surgery procedures between January 2012 and July 2016 at the Inkosi Albert Luthuli Central Hospital in Durban, South Africa. The hospital provides medical and surgical services at a tertiary level to the residents of the KwaZulu-Natal Province, South Africa. Vascular surgery and general surgery patients were selected for this study. as these surgical specialties have been previously associated with a high incidence of poor postoperative patient outcomes at the hospital.[9] In addition to the high incidence of poor postoperative outcomes in both vascular and general surgery populations, it was decided to use both surgical groups to ensure that there was adequate representation of patients who were undergoing major surgery. The unmatched case-control study was conducted using the methodologies suggested by Breslow and colleagues.[10]

Case and Control Definitions

Cases were defined as surgical patients who suffered postoperative MACE while in hospital. Postoperative MACE was determined from hospital discharge summaries and was defined as a diagnosis of myocardial infarction (based on elevated cardiac biomarkers and one of the following: ischemic symptoms, evidence of myocardial ischemia on electrocardiogram, or echocardiographic evidence), stroke (a new onset neurological deficit of vascular etiology of duration ≥24 hours, or resulting in death within 24 hours), or all-cause mortality following surgery, which occurred while patients were still hospitalized. Troponin-I was used as the cardiac biomarker, with a measurement of ≥0.1 ng/ml within the first three postoperative days considered a positive test result. The ECG criteria for MACE included the following: new pathologic Q waves; ST-segment elevation ≥2mm in leads V1, V2, V3, or ≥1mm in other leads; ST-segment depression of ≥1mm; or T-wave inversion of ≥2mm in two contiguous leads. Any new or presumed new cardiac wall motion abnormality was considered a positive echocardiogram result. The choice of this composite outcome is similar to that used in other studies reporting cardiovascular morbidity and mortality following surgery.[11] There is evidence to suggest that there is some cardiovascular involvement in postoperative death of non-cardiovascular etiology,[12] which further supports our decision to use this composite patient outcome. Controls were defined as patients who did not suffer postoperative MACE while in hospital.

Sample Size Calculation

The sample size required for this study was 460 patients (92 cases and 368 controls). This was based on the following parameters: anticipated odds ratio (OR) 2.0 (we considered this to be the smallest clinically significant OR to be detected), estimated exposure of controls 25% (we anticipated that this would be lower than the 50% reported for the general South African adult population, as it was likely that patient HIV serostatus might have been determined at lower level healthcare facilities prior to their admission at the tertiary level facility), alpha risk 5%, power 80%, and a case-control ratio of 1:4. We determined the case pool during the study period to be 100 patients and the control pool to be 2,620 patients. The required number of cases and controls were then selected from each pool using a random number generator to reduce selection bias.

Patient demographics and cardiovascular risk factors

A chart review of case and control patient medical records was conducted. Data related to age, gender, and clinical characteristics comprising Lee's Revised Cardiac Risk Index (RCRI, established risk factors associated with postoperative cardiovascular morbidity and mortality, including history of ischemic heart disease, congestive heart failure, stroke, diabetes, renal impairment, and major surgery).[13] The definitions for the RCRI components were adopted from the original study conducted by Lee and colleagues.[13] The total number of established risk factors present was used to compute the RCRI score for each patient, with each risk factor being allocated a single point. Higher RCRI scores are associated with a higher risk of postoperative cardiovascular morbidity and mortality.[13] HIV serostatus was also determined from the patient medical record. A patient was considered HIV-positive or HIV-negative if they had preoperative documentation of these test results in their medical records. Patients without documented preoperative HIV test results in their medical records were classified as patients with an unknown HIV serostatus in this study. Data extracted from the medical records of each patient were entered onto a password protected database in preparation for statistical analysis.

Statistical Analysis

Data were analyzed in accordance with recommendations for unmatched case-control studies.[10] Univariate (crude) statistical analysis of the study data was conducted using χ^2, Fisher's Exact, or Mann-Whitney tests as appropriate. Results for the univariate analysis are presented as frequencies with

percentages or medians with interquartile ranges (IQR). For the multivariate (adjusted) analysis, an unconditional logistic regression model was used to account for potential confounding in the unmatched case-control study design. All clinical characteristics were entered as independent variables into the logistic regression model, with postoperative MACE being the dependent variable. Results for the multivariate analysis are presented as OR with 95% confidence intervals (95% CI). A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences version 24.0 (IBM Corp., USA).

Study Ethical Approval

Use of patient hospital data for research purposes was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, South Africa.

Results

The characteristics of the study population (combined cases and controls) are shown in Table 1. The median age for the entire study population suggests that many of the patients were middle aged, with a slightly higher proportion of the study population being female. Diabetes, major surgery, and ischemic heart disease were common in the study population (prevalence of 21.3%, 20.2%, and 12.2%, respectively). Fifteen percent of the entire study population was determined to be high risk for postoperative cardiovascular morbidity and mortality (RCRI ≥2 points). HIV serostatus was not known in half of the study population. The proportion of vascular to general surgery patients was 41.3% : 58.7%. The majority of patients in the vascular surgery population had undergone infrainguinal procedures, including lower limb amputation and peripheral arterial bypass grafting. The majority of patients in the general surgery group had undergone open gastrointestinal procedures including cholecystectomy, colorectal resection, and surgery for breast cancer. The incidence of MACE in the vascular surgery group was 21.3%. The incidence of MACE in the general surgery group was 19.3%.

The proportions of several characteristics investigated in this study were statistically higher in cases when compared with controls (p<0.05 at the univariate level of statistical testing, Table 1). These included: older age (p<0.001), male gender (p=0.003), ischemic heart disease (p<0.001), renal impairment (p=0.002), major surgery (p<0.001), and RCRI score ≥2 points (<0.001). There were no differences (at the univariate level of statistical testing) in the proportions of the following characteristics between cases and controls: congestive heart failure (p=0.262), stroke (p=0.569), diabetes (p=0.068), or HIV serostatus (p=0.294).

The results of the multivariate analysis are shown in Table 2. Statistically significant associations at the multivariate level of testing were observed between the following characteristics and postoperative MACE: older age (p<0.001), ischemic heart disease (p=0.004), renal impairment (p=0.013), and major surgery (p<0.001). No statistically significant associations at the multivariate level of statistical testing were observed between any of the remaining characteristics (including HIV serostatus) and postoperative MACE.

Table 1. Respondent Demographics

Characteristic	Sub-Category	Entire Population (n=460)	Cases (n=92)	Controls (n=368)	p-value
Median age in years (IQR)	N/A	51.0 (36.3-64.0)	62.5 (52.3-70.8)	48 (35.0-61.0)	<0.001
Gender					0.003
	Female	239 (52.0)	35 (38.0)	204 (55.4)	
	Male	221 (48.0)	57 (62.0)	164 (44.6)	
Ischemic heart disease					<0.001
	No	404 (87.8)	66 (71.7)	338 (91.8)	
	Yes	56 (12.2)	26 (28.3)	30 (8.2)	
Congestive heart failure					0.262
	No	455 (98.9)	90 (97.8)	365 (99.2)	
	Yes	5 (1.1)	2 (2.2)	3 (0.8)	
Stroke					0.569
	No	440 (95.7)	87 (94.6)	353 (95.9)	
	Yes	20 (4.3)	5 (5.4)	15 (4.1)	
Diabetes					0.068
	No	362 (78.7)	66 (71.7)	296 (80.4)	
	Yes	98 (21.3)	26 (28.3)	72 (19.6)	
Renal impairment					0.002
	No	449 (97.6)	85 (92.4)	364 (98.9)	
	Yes	11 (2.4)	7 (7.6)	4 (1.1)	
Major surgery					<0.001
	No	367 (79.8)	44 (47.8)	323 (87.8)	
	Yes	93 (20.2)	48 (52.2)	45 (12.2)	
RCRI score ≥2 points					<0.001
	No	391 (85.0)	59 (64.1)	332 (90.2)	
	Yes	69 (15.0)	33 (35.9)	36 (9.8)	
HIV serostatus					0.294
	Negative	172 (34.7)	38 (41.3)	134 (36.4)	
	Positive	56 (12.2)	7 (7.6)	49 (13.3)	
	Unknown	232 (50.4)	47 (51.1)	185 (50.3)	

IQR: Interquartile range, N/A: Not applicable, RCRI: Revised Cardiac Risk Index.

Table 2. Characteristics independently/not independently associated with postoperative MACE

Characteristic	Sub-Category	OR (95% CI)	p-value
Age (per year increase)	N/A	1.04 (1.02-1.06)	<0.001
Gender			
	Female	Reference	
	Male	1.72 (0.98-3.01)	0.057
Ischemic heart disease			
	No	Reference	
	Yes	3.48 (1.50-8.07)	0.004
Congestive heart failure			
	No	Reference	
	Yes	3.48 (0.45-26.84)	0.231
Stroke			
	No	Reference	
	Yes	1.50 (0.44-5.06)	0.516
Diabetes			
	No	Reference	
	Yes	1.29 (0.60-2.78)	0.523
Renal impairment			
	No	Reference	
	Yes	5.70 (1.44-22.61)	0.013
Major surgery			
	No	Reference	
	Yes	11.31 (5.68-22.55)	<0.001
RCRI score ≥2 points			
	No	Reference	
	Yes	0.76 (0.30-1.97)	0.578
HIV serostatus			
	Negative	Reference	
	Positive	1.16 (0.42-3.21)	0.780
	Unknown	0.85 (0.47-1.54)	0.599

IQR: Interquartile range, N/A: Not applicable, RCRI: Revised Cardiac Risk Index.

Discussion

Our study findings suggest that an unknown HIV serostatus has no impact on postoperative MACE. There is a possibility that HIV serostatus, irrespective of what it might be, does not have any impact on postoperative cardiovascular outcomes. This possibility was also considered by Redman et al., who found no difference in cardiovascular risk between HIV-positive and HIV-negative vascular surgery patients.[8] Cardiovascular risk in patients with an unknown HIV serostatus was not reported in that study. While our findings confirm those of Redman et al., regarding cardiovascular morbidity and mortality in HIV-negative and HIV-positive patients, our findings appear to add to the findings of their study in that the potential impact of an unknown HIV serostatus on postoperative MACE has now been reported.[8] Therefore, it appears that HIV serostatus does not need to be included in preoperative cardiovascular risk stratification methods in surgical settings with high HIV prevalence. While HIV serostatus might not have been associated with poor outcomes in this study, determination of HIV serostatus in patients for whom it is unknown remains important, as it allows for the identification of HIV-positive patients who might subsequently require antiretroviral therapy.

Increasing age was found to be associated with a higher risk of postoperative MACE in this study. Increasing age is usually associated with the acquisition and increase in severity of comorbidities, including some of those comorbidities associated with cardiovascular complications.[14] Acknowledgement that age might be an important variable to include in cardiovascular risk stratification has also come from the study of Boersma et al., wherein an age-adjusted RCRI is proposed.[15] While we found a crude statistical association between gender and postoperative MACE, adjusted results failed to show any difference in risk of postoperative MACE between male and female patients. This finding is in agreement with findings from cardiovascular risk stratification studies, notably the original RCRI study conducted by Lee and colleagues.[13] Of the six established cardiovascular risk factors, only three were crudely associated with postoperative MACE: ischemic heart disease, renal impairment, and major surgery.[13] These three risk factors were subsequently found to be independent predictors of postoperative MACE. There is research that suggests the clinical importance of risk factors comprising the RCRI might vary between different surgical settings,[16] which could explain why we did not observe all RCRI risk factors to be independently associated with a higher risk of postoperative MACE. This is further supported by our finding that while higher RCRI scores (RCRI scores ≥2 points) were crudely associated with postoperative MACE, this variable was not associated with a higher risk of postoperative MACE when it was included in the multivariate analysis.

There were limitations to this research. A more powerful, true matched case-control study was not feasible, as the sample size calculations revealed there was an insufficient number of cases available in the original registry to conduct the research through this approach. However, there was a sufficient number of cases in the original registry to conduct the research through an unmatched study design. Smoking, hypertension, and hypercholesterolemia were not identified as perioperative cardiovascular risk factors in the study of Lee and colleagues, which is why these variables were not included in the original patient registry and were subsequently absent from our statistical analysis.[13] Another potential reason for the lack of association between RCRI score and MACE in our study could be the modest sample size. This study was conducted at a single, tertiary level hospital and our findings might not be generalizable. A larger study that includes several primary, secondary, and tertiary level healthcare facilities is required. Due to the retrospective nature of our study, we were limited to reporting inpatient outcomes and not outcomes at 30 days postoperatively as done in other prospectively-designed studies of cardiovascular outcomes in surgical populations, such as the VISION study.[12] We recommend prospective research be conducted to measure the association between an unknown HIV serostatus and postoperative MACE within 30 days of surgery.

Conclusion

In summary, we found that an unknown HIV serostatus had no impact on the risk of postoperative MACE in South African surgical patients. Our results suggest that HIV serostatus should not be included in cardiovascular risk stratification methods in surgical settings with a high prevalence of HIV. While HIV serostatus might not have been associated with poor outcomes in this study, determination of HIV serostatus in patients where it is unknown remains important as it allows for the identification of HIV-positive patients who might subsequently require antiretroviral therapy. Increasing age and certain established cardiovascular risk factors appear to be associated with a higher risk of postoperative MACE in South African surgical patients. Further research is required to confirm the findings of our study.

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