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Original Article

Surgical Site Infection and Antimicrobial Resistance Following Resection and Reconstructive Surgery for Oral Cancers: Are We Ready for the Superbugs?

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Abstract

Background: Surgical site infection (SSI) is the most common complication occurring in 19–47% of patients undergoing surgery for head-and-neck cancers. This study aims to assess the predictive factors of SSIs and antibiotic resistance patterns in patients undergoing resection and reconstructive surgery for oral cancers.

Materials and Methods: The clinicopathological data of all patients who underwent surgery for oral cancers at our oncological referral center in South India between October 2014 and May 2019 were reviewed. The differences between groups were compared using independent samples t-test or Mann–Whitney U-test and categorical data were analyzed by Pearson's Chi-square test, Fisher's exact, or continuity correction where appropriate. Receiver operating characteristic (ROC) curve analysis was performed to find the cutoff levels for the various predictors of SSI, using the Youden's index method. A linear regression analysis was done to define the cause-effect relationship of the categorical response variable with explanatory variables.

Results: Of the 135 patients who were studied in our cohort, 43 patients (31.2%) developed SSI. The most commonly isolated organism was *Staphylococcus aureus* (11%; *n* = 15) followed by *Enterococcus* species (4.4%; *n* = 6) followed by coagulase-negative *S. aureus* (3%; *n* = 4) and *Escherichia coli* (37%; *n* = 5). In this study, univariate and multivariate analyses have showed that diabetes mellitus, body mass index (BMI) >25 or <18, neutrophil-to-lymphocyte ratio (NLR) >3.75, platelet-to-lymphocyte ratio (PLR) >137.5, neoadjuvant chemotherapy or radiotherapy, prolonged operative duration, and prolonged anesthesia exposure may render patients more vulnerable to SSI. Moreover, among these parameters, a PLR >137.5, NLR >3.75, and BMI >25 or <18 were found to be highly predictive of SSI. The highly resistant organisms isolated were *S. aureus* and *Enterococcus* species in our study.

Conclusion: The identification of these risk factors in patients undergoing surgery for oral cancers can help in the identification of patients who may be at a higher risk of developing SSI and therefore help in improving the overall outcome, especially in an LMIC setting.

Key words: Oral cancer, Predictive factors, Reconstruction, Surgical site infection

INTRODUCTION

Surgical site infection (SSI) as defined by the Centers for Disease Control and Prevention (CDC) is the infection related to an operative procedure that occurs at or near the surgical incision within 30 days of the procedure, or within 90 days, if a prosthetic material is implanted at surgery. SSI is the most common complication, occurring in 19–47% of patients undergoing surgery for head-and-neck cancers.[1]

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Several studies have suggested various risk factors for the development of SSIs, namely, smoking, alcohol intake, body mass index (BMI), pre-operative anesthesia risk (American Society of Anesthesiologists score), length of pre-operative hospital stay, pre-surgical tracheostomy,

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previous surgery, blood loss, and prior chemotherapy or radiotherapy.[2] Few studies on free flap surgery have reported that flap SSIs were caused by bacteria that are not part of normal flora and many were resistant to the prophylactic antibiotic used.[3]

Existing studies have conflicting results and have imparted little emphasis on independent risk factors and antibiotic resistance pattern. This study aims to assess the predictive factors of SSIs and resistance patterns in patients undergoing resection and reconstructive surgery for oral cancers.

MATERIALS AND METHODS

This study involving a historical cohort was conducted in a high-volume oncology referral hospital in South India in an LMIC setting. After approval by the Institutional Ethics Committee, 135 patients who underwent resection and reconstruction for head-and-neck cancers were recruited between October 2014 and May 2019. Clinicopathological features were analyzed and correlated with SSI.

The compliance of the data to a normal distribution was determined using the Shapiro–Wilk test. Quantitative data are expressed as mean ± standard deviation, median ± interquartile range, or median and range (maximum-minimum). Categorical data are expressed as n (number) or percentage (%). Data were analyzed at a 95% confidence interval, and statistical significance was set at $P < 0.05$. Baseline demographic characteristics, laboratory findings, clinical presentation, bacteriology, and predisposing factors were compared between patients who developed SSI and patients who did not develop SSI. Receiver operating characteristic (ROC) curve analysis was performed to find the cutoff levels for the various predictors of SSI, using the Youden's index method. The differences between groups were compared using Mann–Whitney U-test, and categorical data were analyzed by Pearson's Chi-square test, Fisher's exact, or continuity correction where appropriate. A linear regression test was used to define the cause-effect relationship of the categorical response variable with explanatory variables. All statistical calculations were performed using the Statistical Package for the Social Sciences program (SPSS) version 16 (IBM).

RESULTS

The mean age of the cohort was 59.2 ± 14.9 years, with 76 (56.3%) patients being men. Among them, 43 patients (31.2%) developed SSIs. About 32.6% (n = 14) were diabetics and 20.9% (n = 9) had ischemic heart disease. All patients had a history of tobacco usage. Out of the patients who developed SSIs, 67.4% (n = 29) used chewable forms of tobacco and 27.9% (n = 12) smoked indigenous cigarettes/beedis. Only 4.7% (n = 2) were cigarette smokers. The most common site of lesion was buccal mucosa (38.5%; n = 52), followed by tongue 11.9% (n = 16), retromolar trigone, and the floor of mouth 10.4% (n = 14). About 71.9% (n = 97) of the patients had moderately differentiated squamous cell carcinoma (SCC), 14.1% (n = 19) had poorly differentiated SCC, and 11.1% (n = 15) had well-differentiated SCC. The most common flap used for reconstruction was the pectoralis major myocutaneous flap (51.1%; n = 69) followed by the nasolabial flap (20%; n = 27) and free radial forearm flap (19.3%; n = 26). The other types of flaps that were used were free fibular (5.9%; n = 8) and free anterolateral thigh flap (2.2%; n = 3).

Out of the patients who developed SSIs, the most commonly isolated organism was *Staphylococcus aureus* (11%; n = 15) followed by *Enterococcus* species (4.4%; n = 6) followed by coagulase-negative *S. aureus* (3%; n = 4) and *Escherichia coli* (37%; n = 5). The cultures of nine patients did not show any growth even on delayed incubation. About 46.5% (n = 20) of the patients who developed SSI were found to have highly resistant organisms while 48.8% (n = 21) had heavy growth of the organisms in culture. The highly resistant organisms were seen to be partially sensitive to tigecycline, colistin, or chloramphenicol. The comparison of attributes between patients who developed SSI and did not develop SSI is depicted in Table 1. The ROC curve to find the optimal cutoff ratios for NLR and PLR as predictors of SSI is depicted in Figure 1. Linear regression analysis shows that a PLR >137.5, NLR >3.75, and BMI >25 or <18 could satisfactorily predict the susceptibility of patients to SSI [Table 2]. The predictive power of the model was seen to be 72% (Nagelkerke R Square) and the Hosmer–Lemeshow goodness-of-fit test showed $P = 0.607$, indicating good fit.

DISCUSSION

SSIs are among the most serious but preventable post-operative complications that have shown to significantly increase morbidity and length of hospital stay in patients undergoing head-and-neck surgery.[4] Most SSIs may be attributed to the result of the contamination of surgical wounds from exposure to microorganisms that reside in oral and pharyngeal cavities.[5,6] The majority of published information regarding the predictive factors of SSI in patients with head-and-neck cancer has combined different surgical procedures with multiple surgical classifications; therefore, extrapolating risk factors and antimicrobial recommendations specifically for microvascular reconstructive surgery are controversial. In addition, optimal selection and duration of antibiotic prophylaxis for reconstructive surgery following head-and-neck cancer also remains controversial. In this

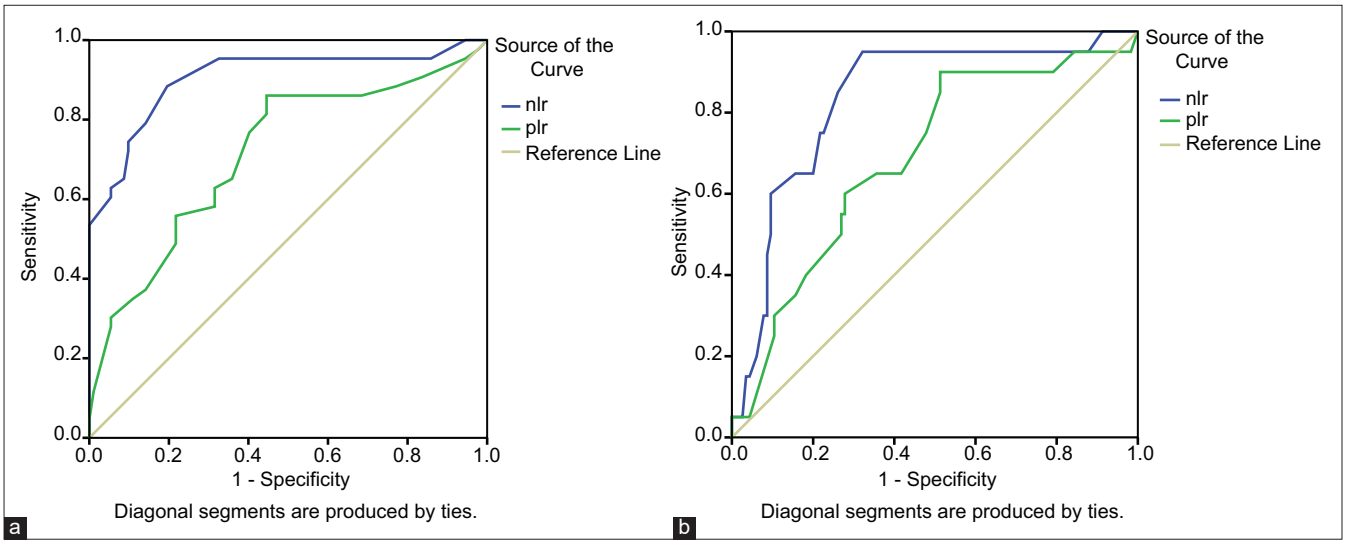

Figure 1: (a and b) Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as predictors of surgical site infections

Table 1: Comparison of attributes between patients who developed surgical site infections versus patients who did not develop surgical site infection

Attribute	Patients who did not develop SSI, *n*=92	Patients who developed SSI, *n*=43	*P* value
Age median (IQR)	55 (17)	62 (22)	0.71
Sex (*n*)	Male: 51 Female: 41	Male: 25 Female: 18	0.85
Diabetes	48.9% (*n*=45)	23.7% (*n*=14)	0.05
Ischemic heart disease	13% (*n*=12)	20.9% (*n*=9)	0.177
Body mass index <18 or >25	0	69.8% (*n*=30)	<0.001
Hemoglobin (g/dl) (Mean±SD)	12±2.01	11.6±2.3	0.17
Neoadjuvant chemotherapy and/or radiotherapy	84.8% (*n*=78)	55.8% (*n*=24)	<0.001
T-stage at presentation (Mean±SD)	2.68±1	2.95±1.01	0.341
Operating time (Mean±SD)	3.9±1.8	4.4±2.4	0.002
Anesthetic time (Mean±SD)	4.8±1.9	5.2±2.8	0.001
Neutrophil-to-lymphocyte ratio (Mean±SD)	3.1±0.7	4.8±1.1	<0.001
Platelet-to-lymphocyte ratio (Mean±SD)	130.5±19.1	149±19.5	0.005

SD: Standard deviation

Table 2: Linear regression analysis of the predictive factors of surgical site infections

Attribute	Unstandardized coefficients		Standardized coefficients	*t*	Sig.
	B	Std. error	Beta		
(Constant)	0.154	0.121		1.281	0.203
PLR >137.5	−0.208	0.057	−0.234	−5.529	0.01
NLR >3.75	0.404	0.057	0.427	7.080	0.000
Previous NACT-RT	−0.073	0.055	−0.068	−1.329	0.186
Body mass index >25 or <18	0.645	0.060	0.576	10.668	0.000
Diabetes	−0.037	0.047	−0.039	−0.774	0.440
Duration of surgery	0.023	0.082	0.100	0.280	0.780
Duration of anesthesia	−0.011	0.078	−0.052	−0.147	0.884

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

study, we analyzed all the possible factors which could predict SSI in patients undergoing resection and reconstructive surgeries for cancers of the oral cavity.

Durand *et al.* concluded that Gram-negative bacilli, Methicillin Resistant *S. aureus* (MRSA), and methicillin-susceptible *S. aureus* (MSSA) were significant SSI pathogens and late onset of infections was common after examining 504 flap surgical cases from 2009 to 2013.[3] Park *et al.* in their retrospective cohort listed that the risk factors are male sex, cardiovascular disease, blood loss >560 ml, and operation time >6 h. They concluded that

the most common pathogen was methicillin-resistant *S. aureus*.[2] A retrospective study of 267 patients done by Zirk *et al*.. (2018) concluded that Gram-positive facultative anaerobic bacteria mainly staphylococcal species were the predominant bacteria in donor site wounds. In addition, this study inferred that the incidence of multidrug-resistant pathogens (*Pseudomonas aeruginosa*) in an acute SSI can be maintained at a very low rate with regular wound dressing.[7]

In addition, Zirk *et al*. (2019), from their retrospective cohort study of 322 patients, demonstrated that smaller tissue transfers are less prone to infections of recipient site and present shorter length of hospital stay.[8] However, significant discrepancies exist between the findings of these studies, and independent risk factors and the pattern of antibiotic resistance still remain unclear.

Lofti *et al*. (2008) noted SSIs in 97 (38.8%) patients out of 258 patients in their prospective study.[9] In 2005, a prospective study done by Penel *et al*. showed that 117 (45%) out of 260 patients developed SSI.[10] Out of 277 patients, 92 patients developed SSI in the study conducted by Hirakawa *et al*., in 2012.[6] However, 21.3% (42) out of 197 demonstrated SSI in a study carried out by Kamizono *et al*.[11] Durand *et al*. in their retrospective cohort study inferred that the *S. aureus* (mainly MRSA or MSSA) were present in 36.6% of the flap SSIs.[3] Park *et al*. in their retrospective cohort study done in 2015 found that the major organism for the causation of SSI was *S. aureus* (32.6%) and 93.2% of *S. aureus* isolates were methicillin resistant.[2]

In this study, univariate and multivariate analyses have showed that diabetes mellitus, BMI >25 or <18, neutrophil-to-lymphocyte ratio (NLR) >3.75, platelet-to-lymphocyte ratio (PLR) >137.5, prior exposure to neoadjuvant chemotherapy or radiotherapy, prolonged operative duration, and prolonged anesthesia exposure may render patients more vulnerable to SSI. Moreover, among these parameters, a PLR >137.5, NLR >3.75, and BMI >25 or <18 were found to be highly predictive of SSI. The highly resistant organisms isolated were *Staphylococcus* and *Enterococcus* species in our study.

CONCLUSION

The identification of these risk factors in patients undergoing surgery for oral cancers along with robust technique and judicious use of antibiotics can help in early identification of patients who may be at a higher risk of developing SSI which may help us improve the overall outcome, especially in an LMIC setting.

The study was approved by the Institutional Ethics Committee of Bharath Hospital and Institute of Oncology (IEC letter no: 4/2019).

AUTHORS' CONTRIBUTIONS

Drs. Bharadhwaj Ravindhran and Hema AM contributed equally to the article and may be credited as joint first authors.

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