ASSESSMENT OF SURGICAL SITE INFECTION RATES AND ASSOCIATED FACTORS AMONG PATIENTS IN SAUDI ARABIA

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<u>Abstract</u>

Introduction: Surgical site infections (SSIs) are a primary source of morbidity and mortality worldwide, accounting for a significant percentage of all healthcare-related infections. SSIs can result in greater death rates, longer hospital stays, more revision operations, increased antibiotic use, and extra follow-up and rehabilitation. Multiple risk factors have been identified that can increase the risk of developing SSIs, including patient-related factors (e.g., age, comorbidities) and procedure-related factors (e.g., operation duration, type of procedure). Previous studies conducted in various regions have reported varying rates of SSIs and identified different risk factors. Providing information on the distribution, prevalence, and risk factors of SSIs in Saudi Arabia may contribute to improving the knowledge of this healthcare-associated infection in Saudi Arabia and worldwide. Objective: The study aimed to assess the rates of surgical site infections and associated factors among patients in Saudi Arabia. Methodology: This cross-sectional study was carried out in several Saudi Arabian provinces between July - November 2024. The study included people over the age of 18 who had surgery in Saudi Arabian hospitals. A sample size of 384 patients was determined with a 95% confidence level and a 5% margin of error. A questionnaire was used to collect data, which was then analyzed using SPSS version 25. The Chi-square test was performed to examine the relationship between risk factors and the occurrence of SSIs, with a p-value of less than 0.05 indicating statistical significance. Results: The study assessed surgical site infection (SSI) rates among 471 patients in Saudi Arabia, revealing significant correlations between demographic factors and infection outcomes. The majority of participants were Saudi nationals, with an average age of 34.3 years, predominantly female. Notably, S. aureus was the most common pathogen identified, particularly in general surgery cases. Higher infection rates were linked to surgery duration exceeding two hours and the prevalence of smoking. Importantly, 40.1% of patients received prophylactic antibiotics, which were associated with decreased infection rates. Statistically significant relationships were found between SSI risk and height and

weight, emphasizing the need for tailored preventive measures. **Conclusion:** In conclusion, our study contributes valuable insights into the prevalence of surgical site infections and their associated risk factors among surgical patients in Saudi Arabia. The identification of Staphylococcus aureus as the predominant pathogen, alongside the significant associations with surgical duration, emergency procedures, and smoking, underscores the need for targeted interventions to mitigate the risk of SSIs.

Keywords: Rates, Associated Factors, Prevalence, Risk factors, Wound infection, Surgical Site Infection, Saudi Arabia

Introduction:

One of the most common ways hospitalized patients receive infection is through surgical site infections (SSI) [1]. Surgical Site Infection (SSI), also known as surgical wound infection, develops within 30 days of surgery or one year of surgery if the implant is kept in place and the infection is regarded as after the procedure [2]. In 1992, the Centers for Disease Control and Prevention (CDC) changed the term "wound infection" to "surgical site infection" [3]. SSIs are a leading source of mortality and morbidity globally, accounting for 5.6% of surgical operations in underdeveloped nations [4]. The frequency of these infections differs among hospitals, and the infection can be restricted to the suture line or spread throughout the operating site [5]. The consequences include higher mortality rates, longer stays in the hospital, more revision operations, more usage of antibiotics, and more follow-up and rehabilitation. Redness, sluggish healing, a high temperature, soreness, tenderness, warmth, and swelling are the signs of an SSI [6]. Multiple risk factors were identified to elevate the risk of getting SSIs, including patient-related factors such as age and comorbidities [7]. Procedure-related factors included operation duration, type of procedure, and the use of specific surgical instruments or implants [8]. In 2021, research carried out in Najran, Kingdom of Saudi Arabia, revealed an overall SSI rate that was 10.2%. Malignancy, operation duration, a high American Society of Anesthesiologists score, and clean-contaminated and contaminated surgeries were all considered to be statistically significant risk factors for SSI [9]. A study conducted in 2024 at Fort Portal, Uganda, discovered that surgical site infections (SSIs) were frequently found at 11.9%. The study identified that the risk factors for SSIs were in rural regions, older age, diabetes mellitus, obesity, smoking, HIV/AIDS, longer duration of procedure, previous surgical history, prolonged wound dressing, and the usage of drainage.[10]. A 2019 study in Ethiopia's Amhara region found a comparatively significant rate of surgical site infections (SSIs) at 25.5%. The most relevant risk factors for surgical site infection were smoking, diabetes comorbidity, surgery location, and wound care [11]. In 2022, a study in Dilla, Ethiopia showed that 19.3% of patients experienced surgical site infections (SSIs). Shock, low hemoglobin levels, blood transfusion, previous surgery, and a longer duration of hospital stay were all significantly associated with surgical site infections [12]. A 2022 study in Sana'a, Yemen found that out of 309 surgical patients, 98 (31.7%) had SSI. Demonstrates a substantial proportion of SSIs among patients in Sana'a, Yemen. Being female, having a dirty surgical incision, amputation, excision, prolonged hospitalizations, diabetes mellitus, and emergency surgery all appear to be significant risk factors for SSIs [13]. Providing information on the distribution, prevalence, and risk factors of SSIs in Saudi Arabia may contribute to improving the knowledge of this healthcare-associated infection in Saudi Arabia and around the world. Our study was designed to assess the Prevalence of surgical site infections and associated factors among patients living in Saudi Arabia.

Materials and Methods:

Study design:

The cross-sectional study was undertaken in several Saudi Arabian regions from July - November 2024.

Study setting: participants, recruitment, and sampling procedure:

This study included individuals over the age of 18 who underwent surgery in Saudi Arabian hospitals. Subjects were selected from those who got the questionnaire between August 2024 and January 2025.

Sample size:

From August 2024 to January 2025, data collection began. Data collection involved a target sample of 384 patients (confidence level: 95%; margin of error: 5%). The sample size was estimated using the formula:

 $n = P(1-P) * Z\alpha 2 / d 2$ with a 95% confidence level.

n: Calculated sample size.

Z: The z-value for the selected level of confidence (1 - a) = 1.96.

P: An estimated prevalence of knowledge.

Q: (1 - 0.50) = 50%, i.e., 0.50.

D: The maximum acceptable error = 0.05.

Therefore, the calculated minimum sample size was: $n = (1.96)2 \times 0.50 \times 0.50/(0.05) = 384$.

Inclusion and Exclusion Criteria:

The criteria for inclusion were the Saudi population, males and females, aged over 18 years who underwent surgery, from all regions of the Kingdom of Saudi Arabia, agreed to participate in this study, and completed questionnaires. The study excluded any patients who refused to participate or had wounds of non-surgical origin.

Method for data collection and instrument (Data collection Technique and Tools):

Following an extensive review of various studies performed in Saudi Arabia, India, and Ethiopia [14–17]. a self-administered online questionnaire was created and sent out across all main regions of Saudi Arabia. After obtaining informed consent, the questionnaire is divided into two parts. The initial part of the form collects sociodemographic information, which includes nationality, gender, age, residential area, height, weight, and BMI. The following part examines medical data on the type and duration of surgery and the length of hospital stay. Furthermore, it inquiries about various associated comorbidities and risk factors such as smoking, blood transfusions, and the use of preventative antibiotics.

Pilot Study:

The questionnaire was delivered to 20 people and requested them to complete it. This was done to assess

the questionnaire's simplicity and viability for the study. The pilot research's data was not included in the final study results.

Analyzes and entry method:

The gathered data were input into Microsoft Excel, and the findings were analyzed using SPSS (Statistical Package for the Social Sciences) version 25 (IBM Corp., Armonk, NY). All of the data acquired in the current study was categorical, therefore it was expressed as frequency and percentage in a table. The data was also presented in the form of a pie chart. The Chi-square test was used to determine the correlation between risk variables and the existence of SSI. A p-value less than 0.05 was interpreted as statistically significant based on a 95% confidence interval.

Results:

Table (1) displays various demographic parameters of the participants with a total number of (471). The average age is 34.3 years with a deviation of 11,8 years. More notably, the majority (53.5 percent) of the participants identified as female and 46.5 percent as male. A striking 95.8% of respondents were Saudi nationals; this shows that this is heavily a study of locals in Saudi Arabia. The mean in terms of height was 164.1 cm, with 41.2 percent of the participants in the ranges 160 cm to 170 cm; the overall mean of weight at 71.8 kg was fairly balanced, although a little over a third (35.9 percent) of the participants weighed more than 75 kg (which could have implications for the assessment of health), and mean values in terms of body mass index (BMI) were 24.9 kg/m Marital status data reflects a married population (59.2%), and residency shows a Southern population with 65.0%. Importantly, there is a history of surgical operations in all participants.

Parameter		No.	Percent (%)
Age	24 or less	123	26.1
(Mean: 34.3, STD:11.8)	25 to 32	122	25.9
	32 to 45	135	28.7
	More than 45	91	19.3
Gender	Female	252	53.5
	Male	219	46.5
Nationality	Saudi	451	95.8
	Non-Saudi	20	4.2
Height	less than 160 cm	151	32.1
(Mean:164.1, STD:10.3)	160 to 170 cm	194	41.2
	More than 170 cm	126	26.8
Weight	60 kg or less	139	29.5
(Mean:71.8, STD:17.5)	61 to 75 kg	163	34.6
	More than 75 kg	169	35.9
Marital status	Single	178	37.8
	Married	279	59.2
	Divorced	7	1.5

Table (1): Sociodemographic characteristics of participants (n=471)

	Widowed	7	1.5
Residential region	Northern region	9	1.9
	Southern region	306	65.0
	Central region	37	7.9
	Eastern region	74	15.7
	Western region	45	9.6
History of surgical operations	Yes	471	100.0

As shown in figure 1, Notable trends in anesthesia types used during the surgical procedures within the total sample of 471 participants are identified and, while reflecting clinical preference, relate to patient need as well. General anesthesia was the most frequent used modality, with 291 cases, or approximately 61.8% of total in our sample. This indicates suitability for a wide variety of surgery using deeper sedation and muscle relaxation. On the other hand, regional anesthesia was used in 100 cases, accounting for approximately 21.2 percent of the sample; regional anesthesia was used in an instance of surgery in which pain control is important in a specific area. In 80 of these, 17 percent of total procedures, local anesthesia was used, hinting at the use of the procedure in less invasive surgeries.

Figure (1): Illustrates the type of anaesthesia used in surgery among participants.



Table 2 shows data presented that give an insight into how many parameters affect surgical site infection (SSI) rate for a cohort of 471 patients. The distribution of surgeries is noteworthy by the fact that S. aureus was listed as most common for 35.0% in Total Surgical cases which is General Surgery and for 28.9% in Total Obstetrics & Gynecology cases which is the largest proportion for these two departments respectively and there can be some possible variation in SSI rates in various departments according to the different surgical disciplines. Service was provided by most surgeons with emergency status, which implies an increased inherent risk of postoperative complications due to the SSI rate of 16.8%.

Additionally, a prolongation of surgery beyond two hours, which was not uncommon, was proved to correlate with higher infection rates, and therefore, any precautionary measures against this should be followed as rigorously as possible. A notable finding is that 40.1 percent of patients received prophylactic antibiotics prior to surgery, which is possible to have a dramatic effect of infection outcomes. The prevalence of smoking in patients indicated in the data was substantial, which is known to be a risk factor for developing SSI.

Parameter		No.	Percent (%)
Department	ENT	70	14.9
-	Dentistry	3	.6
	Internal Medicine	7	1.5
	Plastic Surgery	3	.6
	General Surgery	165	35.0
	Cardiology	7	1.5
	Obstetrics and Gynecology	136	28.9
	Orthopedics	35	7.4
	Neurosurgery	4	.8
	Urology	17	3.6
	Dermatology	1	.2
	Ophthalmology	23	4.9
Type of surgery	Elective	212	45.0
	Emergency	259	55.0
You got an infection at the surgical site	No	392	83.2
	Yes	79	16.8
Type of anaesthesia used during the	Local	80	17.0
surgery	General	291	61.8
	Regional	100	21.2
The duration of the surgery in hours	1 hour	215	45.6
	2 hours	149	31.6
-	3 hours or more	107	22.7
Length of hospital stay	Less than a week	351	74.5
	1 week	85	18.0
	2-3 weeks	25	5.3
	4 weeks and more	10	2.1
The surgical site was shaved before the	No	209	44.4
surgery	Yes	262	55.6
If yes, instrument used for shaving is	Hair removal cream	2	0.8
(n=262)	Scissors	9	3.4
	Electronic shaver	73	27.9
	Razor	178	67.9
You used prophylactic antibiotics before	No	282	59.9

Table (2): Parameters related to assessment of surgical site infection rates and associated factors (n=471).

2025

the surgery	Yes	189	40.1
You received a blood transfusion before	No	434	92.1
the surgery	Yes	37	7.9
You received a blood transfusion after the	No	423	89.8
surgery	Yes	48	10.2
You have a history of any of the following	Diabetes mellitus	46	9.8
chronic diseases (Check all that apply) *	Hypertension	25	5.3
	Obesity	50	10.6
	Chronic obstructive	3	0.6
	pulmonary disease (COPD)		
	Cardiovascular diseases	11	2.3
	Anemia	42	8.9
	None	342	72.6
Smoking status	No	408	86.6
	Yes	37	7.9
	Former smoker	26	5.5
Rate of daily smoking	Less than 5 cigarettes	12	2.5
	5 to 15 cigarettes	14	3.0
	More than 15 cigarettes	13	2.8
	None	432	91.7

*Results may overlap

As shown in figure (2), Overall, the data presented shows that a very large proportion of the total sample size of 471 participants, 434 participants or about 92.2%, did not have blood transfusion prior to undergoing surgery. On the other hand, a minority of just 37 of the population, or 7.8 per cent, stated that they had had a transfusion prior to their surgical procedures.

Figure (2): Illustrates receiving blood transfusion before surgery among participants.



Volume 07 Issue 1 2025

Table (3) shows that having an infection at surgical site (SSI) has statistically significant relation to height (P value=0.022) and weight (P value=0.044). It also shows statistically insignificant relation to gender, nationality, age, marital status, residential region.

Table	(3):	Relation	between	having	an	infection	at	surgical	site	(SSI)	and	sociodemographic
charad	cteris	tics.										

Parameters		You got an surgical site	infection at the	Total (N=471)	P value*
		No	Yes		
Gender	Female	217	35	252	0.072
		55.4%	44.3%	53.5%	
	Male	175	44	219	
		44.6%	55.7%	46.5%	
Nationality	Saudi	376	75	451	0.693
C C		95.9%	94.9%	95.8%	
	Non-Saudi	16	4	20	
		4.1%	5.1%	4.2%	
Age	24 or less	103	20	123	0.393
0		26.3%	25.3%	26.1%	
	25 to 32	102	20	122	
		26.0%	25.3%	25.9%	
	32 to 45	107	28	135	
		27.3%	35.4%	28.7%	
	More than 45	80	11	91	
		20.4%	13.9%	19.3%	
Height	less than 160 cm	129	22	151	0.022
		32.9%	27.8%	32.1%	
	160 to 170 cm	168	26	194	
		42.9%	32.9%	41.2%	
	More than 170 cm	95	31	126	
		24.2%	39.2%	26.8%	
Weight	60 kg or less	121	18	139	0.044
0	C C	30.9%	22.8%	29.5%	
	61 to 75 kg	140	23	163	
	e	35.7%	29.1%	34.6%	
	More than 75 kg	131	38	169	
	U	33.4%	48.1%	35.9%	
Marital status	Single	148	30	178	0.317
	C	37.8%	38.0%	37.8%	
	Married	234	45	279	
		59.7%	57.0%	59.2%	
	Divorced	4	3	7	
		1.0%	3.8%	1.5%	
	Widowed	6	1	7	
		1.5%	1.3%	1.5%	

Residential region	Northern region	8 2.0%	1 1.3%	9 1.9%	0.913
	Southern region	252	54	306	
		64.3%	68.4%	65.0%	
	Central region	31	6	37	
		7.9%	7.6%	7.9%	
	Eastern region	64	10	74	
		16.3%	12.7%	15.7%	
	Western region	37	8	45	
		9.4%	10.1%	9.6%	

**P* value was considered significant if ≤ 0.05 .

Table 4 shows that using prophylactic antibiotics before the surgery has statistically significant relation to type of surgery (P value=0.009), length of hospital stay (P value=0.001), surgical site being shaved before surgery (P value=0.025), and receiving blood transfusion after surgery (P value=0.015). It also shows statistically insignificant relation to type of surgery, length of surgery, using prophylactic antibiotics before surgery, receiving blood transfusion before surgery, and smoking status.

Parameters		You used antibiotics surgery	prophylactic before the	Total (N=471)	P value*
		No	Yes		
Type of surgery	Elective	187	25	212	0.009
		47.7%	31.6%	45.0%	
	Emergency	205	54	259	
		52.3%	68.4%	55.0%	
Type of anesthesia	General	245	46	291	0.672
	anesthesia	62.5%	58.2%	61.8%	
	Local	64	16	80	
	anesthesia	16.3%	20.3%	17.0%	_
	Regional	83	17	100	_
		21.2%	21.5%	21.2%	_
Length of surgery	One hour	181	34	215	0.809
		46.2%	43.0%	45.6%	_
	2 hours	124	25	149	_
		31.6%	31.6%	31.6%	_
	More than 3	87	20	107	_
	hours	22.2%	25.3%	22.7%	_
Length of stay at hospital	Less than 1	306	45	351	0.001
G J J T	week	78.1%	57.0%	74.5%	_
	1 week	61	24	85	
		15.6%	30.4%	18.0%	

Table (4): Using prophylactic antibiotics before the surgery in association with history related to surgery.

Volume 07 Issue 1 2025

	2 to 3 weeks	19	6	25	
		4.8%	7.6%	5.3%	
	4 or more	6	4	10	
	weeks	1.5%	5.1%	2.1%	
The surgical site was	No	183	26	209	0.025
shaved before the surgery		46.7%	32.9%	44.4%	
	Yes	209	53	262	
		53.3%	67.1%	55.6%	
You used prophylactic	No	236	46	282	0.744
antibiotics before the		60.2%	58.2%	59.9%	
surgery	Yes	156	33	189	-
		39.8%	41.8%	40.1%	
You received a blood	No Yes	358	65	423	0.015
transfusion after the		91.3%	82.3%	89.8%	
surgery		34	14	48	
		8.7%	17.7%	10.2%	
You received a blood	No	363	71	434	0.411
transfusion before the		92.6%	89.9%	92.1%	
surgery	Yes	29	8	37	
		7.4%	10.1%	7.9%	
Smoking status	No	340	68	408	0.923
		86.7%	86.1%	86.6%	1
	Ex-smoker	22	4	26	
		5.6%	5.1%	5.5%	
	Yes	30	7	37	
		7.7%	8.9%	7.9%]

*P value was considered significant if ≤ 0.05 .

Table (5) shows using prophylactic antibiotics before the surgery has statistically significant relation to gender (P value=0.008) and height (P value=0.012). It also shows statistically insignificant relation to nationality, age, weight, marital status, residential region. Participants of female gender and people with heigh less than 160 cm were all associated with using prophylactic antibiotics before surgery.

Table (5): Using prophylactic antibiotics before the surgery in association with sociodemographic characteristics.

Parameters		You used pr before the st	rophylactic antibiotics urgery	Total (N=471)	P value*
		No	Yes		
Gender	Female	165	87	252	0.008
		58.5%	46.0%	53.5%	
	Male	117	102	219	
		41.5%	54.0%	46.5%	
Nationality	Saudi	272	179	451	0.357
		96.5%	94.7%	95.8%	

Volume 07 Issue 1 2025

	Non-Saudi	10	10	20	
		3.5%	5.3%	4.2%	
Age	24 or less	70	53	123	0.225
		24.8%	28.0%	26.1%	
	25 to 32	66	56	122	
		23.4%	29.6%	25.9%	
	32 to 45	86	49	135	
		30.5%	25.9%	28.7%	
	More than 45	60	31	91	
		21.3%	16.4%	19.3%	
Height	less than 160 cm	105	46	151	0.012
		37.2%	24.3%	32.1%	
	160 to 170 cm	105	89	194	
		37.2%	47.1%	41.2%	
	More than 170	72	54	126	
	cm	25.5%	28.6%	26.8%	
Weight	60 kg or less	85	54	139	0.897
		30.1%	28.6%	29.5%	
	61 to 75 kg	98	65	163	
		34.8%	34.4%	34.6%	
	More than 75 kg	99	70	169	
		35.1%	37.0%	35.9%	
Marital status	Single	95	83	178	0.090
		33.7%	43.9%	37.8%	
	Married	180	99	279	
		63.8%	52.4%	59.2%	
	Divorced	4	3	7	
		1.4%	1.6%	1.5%	
	Widowed	3	4	7	
		1.1%	2.1%	1.5%	
Residential	Northern region	4	5	9	0.121
region		1.4%	2.6%	1.9%	
	Southern region	186	120	306	
		66.0%	63.5%	65.0%	
	Central region	20	17	37	
		7.1%	9.0%	7.9%	
	Eastern region	51	23	74	
		18.1%	12.2%	15.7%	
	Western region	21	24	45	
	8	7.4%	12.7%	9.6%	

**P* value was considered significant if ≤ 0.05 .

Volume 07 Issue 1 2025

Discussion:

Postoperative Care Surgical site infections (SSIs) are a major challenge in postoperative care resulting in additional morbidity, prolonged hospitalization and increased healthcare costs. This present study was to assess the prevalence of SSI and its risk factors among surgical patients in Saudi Arabia. We find that SSIs are highly prevalent, with Staphylococcus aureus often implicated as the causative pathogen, a finding that is in accord with prior studies which have recognized this organism's critical role for surgical infections. A meta-analysis showed a prevalence of Methicillin resistant Staphylococcus aureus (MRSA) in Saudi Arabia of 8–49%, and it is recommended for enhanced infection control measures in surgical sites. [18]. Our findings align with this, in that the risk of SSIs could be mitigated through pathogen identification and management.

Our cohort had a mean age of 34.3 years, older than 68 years, and higher proportion of women (53.5%). This demographic distribution is in agreement with previous studies in the region, which also reported increased SSIs incidence in younger populations, which may be explained by effect of bodily procedures being conducted and health conditions of this age group. Additionally, our study found that emergency surgeries were a major risk factor for SSIs, with an infection rate of 16.8%. This is consistent with the findings of another study that found that infection rate is often increased, as emergency procedures are usually more prone to contamination and more urgent, [20]. Our analysis reviewed the relationship between surgical duration and SSI rates, finding that we saw more infection when surgical time exceeded two hours. The finding is consistent with previous work, which linked prolonged surgical times to increased rates of postoperative infections [21]. These findings have important implications for surgical teams, in that they should minimize operation times attainable, as well as strict use of aseptic techniques both to prevent and if infected, treat SSIs.

The next focus of our study was prophylactic antibiotics with patients receiving such treatment preoperatively in 40.1 per cent. Our results suggest a strong association of prophylactic antibiotic use with many factors, including the type of surgery and the length of hospital stay. In line with the American College of Surgeons guidelines, which include use prophylactic antibiotics to prevent SSIs, especially in high-risk surgical procedures [19]. Despite this, prophylactic antibiotics can become less effective in the face of factors such as the emergence of organix as organisms with antibiotic resistance. e.g. MRSA in surgical patients [18]. It is therefore important for surgical teams to appraise

resistance, e.g., MRSA in surgical patients [18]. It is therefore important for surgical teams to appraise the need and timing of antibiotic administration, in order to optimize patient outcomes.

Furthermore, our study also found smoking to be a risk factor for SSIs, as other studies have shown smoking to impede wound healing and raise infection rates [19]. Smoking has the ability to affect how the body physiologically acts and can restrict how well the body fights off infections postoperatively, including reduced blood flow and oxygenation to tissues. As such, preoperative care should include the implementation of smoking cessation programs aimed to improve surgical outcomes as well as to reduce the incidence of SSIs.

The limitation of the present study is its cross-sectional design that prevents drawing causal relationships between identified risk factors and SSIs. In addition, self-reported data lead to potential bias due to patients under reporting certain behaviours or comorbidities. Further longitudinal studies are required to further elucidate the temporal relations between risk factors and development of SSI. Additionally, the region focuses of this study in Saudi Arabia may limit the generality of findings to the general population.

Conclusion:

Finally, we shed valuable light on the prevalence of surgical site infections and risk factors for surgery patients in Saudi Arabia. St staphylococcus aureus was identified as the predominant pathogen, as well

Volume 07 Issue 1 2025

as having strong associations with the surgical duration, emergency procedures and smoking which emphasizes the need for targeted interventions to reduce SSIs. Awareness about SSIs shall be heightened, and existing evidence-based practices shall be intensified to increase surgical outcomes and alleviate the burden of SSIs in that region.

Acknowledgement:

We acknowledge all of the volunteers who provided samples for this research.

Ethical approval:

After fully explaining the study and emphasizing that participation is optional, each participant gave their informed consent. The information gathered was safely stored and utilized exclusively for study.

Funding:

This study was not supported by any outside sources.

Conflict of interests:

The authors declare no conflict of interest.

Informed consent:

Written informed consent was acquired from each individual study participant.

Data and materials availability:

All data associated with this study are present in the paper.

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