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An exploratory study of knowledge, attitudes, and practices toward HPV associated anal cancer among Pakistani population

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Background: Anal cancer, mainly attributed to human papillomavirus (HPV) infection, is rising in prevalence among the general population in Pakistan. This study aimed to examine the knowledge, attitudes, and practices (KAP) towards anal cancer screening and HPV of the general population in Pakistan.

Method: We surveyed anal cancer KAP using social media and snowball sampling from December 2022 to May 2023. The questionnaire had 16 knowledge, 12 attitudes, 6 practice questions, and socio-demographic variables. We applied validity criteria for inclusion and exclusion and used cutoffs \geq 50% for each KAP category. We analyzed data in R with Guttman's λ 2 for reliability, did univariate and bivariate analysis, and reported frequencies, percentages, p-values, coefficients, odds ratios, and 95% confidence intervals.

Results: We surveyed 1620 people and discovered low awareness of HPV and anal cancer causes prevention, and screening (11%-24%), high stigma and embarrassment for screening (54%-70%), strong moral beliefs (89%), condom nonuse (91%), and low engagement in health services and programs (9.1%-14%). Knowledge (75.23%, OR = 1.0984, p = 0.05) was shaped by socio-demographic factors, attitude, and practice, with higher education enhancing knowledge (OR = 1.0984, p = 0.05). Attitude (78.45%, OR = 6.6052, p< 0.001) was influenced by socio-demographic factors, practice, and knowledge as well. Younger females, single, unemployed, students, living with more family members, earning more income, and residing in Islamabad had a more positive attitude (ORs from 1.0115 to 6.6052, p< 0.05), while religion did not affect attitude (p = 0.51). Practice

(9.16%, OR = 0.1820, p< 0.001) was determined by socio-demographic factors, knowledge, and attitude. Older males, employed teachers, living with more family members, earning less income, and residing in Islamabad had better practice (ORs from 0.1323 to 3.8431, p< 0.05), but marital status and religion did not influence practice (p > 0.05).

Conclusion: Pakistani young adults need more education, awareness, health services, and programs on HPV and anal cancer, as they have low awareness, high stigma, and socio-cultural challenges. In addition, it is recommended for more research and policy initiatives are needed to address socio-cultural factors and increase anal Pap to overcome anal cancer.

KEYWORDS

human papillomavirus, anal cancer screening, HPV vaccine, anal pap test, Pakistan, public health, immunization, healthcare

1 Introduction

Human Papillomavirus (HPV) infection is the most prevalent sexually transmitted infection (STI) worldwide (1, 2) and can cause both benign (anogenital warts) and malignant lesions (penile, anal, and oropharyngeal malignancies) (3). HPV subtypes differ in their genetic sequence and are categorized as low-risk or high-risk based on their oncogenic potential (4-6). Additionally, 14 HPV types are designated as human carcinogenic, including high-risk HPV (HR-HPV; HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) (7, 8). High-risk HPV strains, predominantly 16 and 18, are responsible for almost all cervical cancer cases. A persistent high-risk HPV16 infection is associated with 86 to 100% of anal malignancies and some head and neck cancers (9). High-grade squamous intraepithelial lesions (HSIL), a precancerous condition that can advance to anal cancer, also predominantly involve HPV16 (2, 9, 10). These HPV subtypes are often associated with anogenital cancers but usually do not produce noticeable warts; therefore, HPV infection may remain unnoticed (11, 12).

HPV causes around 48.6% of the annual cases of anal cancer in men (13). However, the rising rates of anal cancer may be associated with the higher number of sexual partners and the more frequent practice of anal intercourse in the past few decades (14, 15). Pakistan is a diverse and complex country where many different ethnic groups live across vast geographic areas. Each group has distinct characteristics and health risks, which may affect their cancer outcomes. However, the country lacks a unified system for collecting and reporting cancer data, which makes it difficult to obtain accurate and reliable estimates of cancer incidence and prevalence. The existing research on cancer in Pakistan is often based on regional data, which may not reflect the true picture of the whole country or account for the variations among different ethnic groups, and the available data is only hospital-based (16). According to International Agency for Research on Cancer (IARC), in 2020, Pakistan had crude incidence rates of anal cancer of 0.34 and 0.17 per 100,000 for men and women, while age-standardized incidence rates of 0.46 and 0.22 per 100,000 for men and women, respectively (17).

Pakistan is a country where Islam shapes society's moral and social fabric. Any sexual activity outside the marital bond, especially homosexual sex, is considered a grave sin and a violation of Islamic law. Many Pakistanis also assume that HIV cannot affect them, as they believe Muslims are immune to this disease associated with illicit sex (18, 19). However, this assumption is challenged by the rising number of HIV cases in Pakistan, which reached 8,262 from January to September 2022 (20). The main mode of HIV transmission in Pakistan is sexual contact, especially among men who have sex with men (MSM). MSM in Pakistan includes various groups, such as seamen, prisoners, drug addicts, truck drivers, migrant men, male prostitutes, hijras (transvestites), zenanas (she-males), maalishias (masseurs), and chavas (men who swap sexual roles) (21-24). These groups are highly vulnerable to HIV infection due to their risky sexual behaviors and lack of access to prevention and treatment services. The current HIV epidemic in Pakistan is a wake-up call for the public and the authorities to recognize and address the hidden reality of MSM and their sexual health needs.

Given the increasing burden of sexually transmitted diseases in Pakistan, it is imperative to investigate the basic knowledge and awareness of the population about anal cancer. However, there is a dearth of research on this topic in Pakistan, and the level of awareness and prevention of anal cancer among the public is unknown. Therefore, this study is the first of its kind in Pakistan, aiming to explore the knowledge, attitudes, and practices (KAP) regarding HPV-associated anal cancer in the community.

2 Methods

2.1 Study design

We used an anonymous online questionnaire to collect the data for this study, which evaluated the public's knowledge, attitudes, and practices concerning anal cancer. We employed a snowball sampling technique to distribute the questionnaire link through various social media platforms, such as WhatsApp, Twitter, Facebook, Messenger, Gmail, and Instagram. The respondents had to answer every item on the questionnaire, which was available in both English and their native language. The data collection period for this study spanned seven months, from December 2022 to May 2023. The participants completed the questionnaire voluntarily after receiving information about the nature of the study and assurance of anonymity and confidentiality of responses. The study encompassed all the regions of Pakistan, including Khyber Pakhtunkhwa (KPK), Punjab, Balochistan, Sindh, Gilgit-Baltistan (GB), Azad Jammu Kashmir (AJK), and Islamabad Capital Territory (ICT), as illustrated in Figure 1.

2.2 Inclusion and exclusion criteria

This study aimed to assess the Pakistani population's KAP parameters on a large scale, regardless of gender and residence. The study included respondents who met the following criteria: (i) they were 10 years old or above, and (ii) they were residents of Pakistan. These criteria were consistent throughout the study. To ensure the validity and relevance of our study, we excluded respondents who met any of the following criteria: (i) had a history of allergy to the HPV vaccine and could not receive immunization, (ii) the respondent was a foreign citizen studying or living in Pakistan, and (iii) had HPV-associated malignancy, as their personal experience might bias opinions.

2.3 Measurements

The questionnaire was developed by adapting previously validated questionnaires to the study's context (25-31). We

measured the respondents' knowledge of HPV using 16 questions encompassing various topics such as clinical features of anal cancer, viral structure, transmission modes, anal cancer prevention, anal screening, treatment options, and vaccination information. All respondents could opt for "Yes," "No," or "Not Sure." The knowledge scores were derived by allocating one point to each correct answer, resulting in a total score ranging from 0 to 16. A cutoff of \geq 50% (eight) was applied to distinguish knowledgeable and not-knowledgeable respondents, with higher scores indicating better knowledge.

Furthermore, we investigated the attitudes toward HPV using 12 questions about individual beliefs, perceptions about anal screening, and willingness toward HPV vaccination. The responses were categorized as "Yes," "No," and "Not Sure." Likewise, the overall attitude was divided into positive and negative scales. The attitude score was obtained by giving one point to "Yes" as the positive attitude and zero points to "No" and "Not Sure" as the negative attitude. A cutoff of six was applied to differentiate positive and negative attitudes, with equal or higher scores indicating a positive attitude and lower indicating a negative attitude.

Additionally, we appraised the practices of participants using 6 questions about screening for anal cancer, participation in HPV awareness campaigns, and safe sex practices. Respondents were asked to answer using the "Yes" and "No" scales, and one point was awarded for good practices. A cutoff of six was applied to classify "good practice" and "poor/bad practices", where scores equal or above the cutoff indicated good practice while low scores indicated poor/bad practices. Finally, we collected a broad range of socio-demographic variables, including gender, age, marital status, employment status, occupation, number of family members, level of education, religion, monthly household income, and place of residence to categorize their knowledge, attitudes, and practices in different variables, as illustrated in Table 1.



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2.4 Ethical approval

Ethical approval was obtained from the Departmental Bioethical Committee of The University of Haripur (UOH-RC-EA-142). Informed consent was taken from all participants before they participated in the study. In the case of participants under 18 years old, the participant's legal guardian provided written informed consent to participate in this study.

2.5 Statistical analysis

We stored the raw data in an Excel file and imported it into R version 4.2.2 for analysis. We used different R packages (gtsummary, ggplot2, and circlize) to clean and screen the data and to estimate the reliability of the test items; in addition, we adopted Guttman's λ_2 (32) instead of Cronbach's alpha. Guttman's λ_2 was used to estimate the reliability of the questionnaire, as it does not require the assumptions of Cronbach's alpha, such as uncorrelated errors, identical covariances between items, and uni-dimensionality, which are often violated. We obtained a Guttman's λ_2 value of 0.86, indicating that 86% of the variance was due to true scores and 14% was due to error. Univariate descriptive analysis was performed to summarize the frequency (n) and percentages (%) for each category of the variables under consideration (see Tables 1-4). We also conducted bivariate descriptive analysis to examine the relationship between socio-demographic and main variables (i.e., knowledge, attitudes, and practices). We reported the frequency (n) and percentages (%) for each sub-category among both variables. Furthermore, the Chi-square test was used to check the association between variables and reported the results in terms of the p-value, where a p-value< 0.05 indicated a significant association between the responses of considered variables. Finally, we attempted binary logistic regression, and interpreted the model using regression coefficient values, the pvalue of coefficients, odds ratio (OR), and 95% confidence interval (CI) (see Tables 5-7).

3 Results

3.1 Socio-demographic characteristics of study participants

Table 1 provides a comprehensive overview of the demographic and socio-economic characteristics of 1620 participants. Amongst, the participants were predominantly young (53.8% aged 21-30), female (61.2%), single (80.5%), unemployed (70.6%), students (67.9%), and had large families (72.3% had four or more family members). In addition, most of the participants did not disclose their income (59.5%), had a university education (66.9%), were Muslim (99.3%), and lived in KPK province (59.8%). Moreover, we

TABLE 1 Demographics of participants (N = 1620).

Variables		Frequency (n= 1620)	Percent (%)	
	10-20	532	32.8	
	21-30	872	53.8	
Age (years)	31-40	196	12.1	
	41-50	12	0.7	
	>50	8	0.5	
	Male	628	38.8	
Gender	Female	992	61.2	
	Single	1304	80.5	
	Married	300	18.5	
Marital Status	Widowed	4	0.2	
	Divorced	12	0.7	
P 1	Employed	476	29.4	
Employment	Unemployed	1144	70.6	
	Business	44	2.7	
	Other	132	8.1	
Occupation	Employed	144	8.9	
	Teacher	200	12.3	
	Student	1100	67.9	
	≤ 2	108	6.7	
Family Members	3	340	21.0	
	≥ 4	1172	72.3	
	≤50,000	248	15.3	
T	51,000-80,000	188	11.6	
Income	>80,000	220	13.6	
	Not disclosed	964	59.5	
	Primary school	16	1.0	
Education	High school	520	32.1	
	University	1084	66.9	
D !: :	Non-Muslim	12	0.7	
Keligion	Muslim	1608	99.3	
	ICT	134	8.3	
	AJK/GB	146	9.0	
Resident (Province)	Sindh	149	9.2	
()	Punjab	223	13.8	
	КРК	968	59.8	

evaluated KAP parameters using different questionnaires that clearly demonstrate our findings, as shown in Figure 2.

TABLE 2 Knowledge questionnaire responses.

		Response	2
Questions	No	Not sure	Yes
Anal cancer is more common in men than in women?	40	252	1,328
	(2.5%)	(16%)	(82%)
Can HPV cause penile cancer in males?	116	584	920
	(7.2%)	(36%)	(57%)
Can medications cure HPV infections?	188	928	504
	(12%)	(57%)	(31%)
Do you think the HPV vaccine is available in Pakistan?	68	544	1,008
	(4.2%)	(34%)	(62%)
Does sexual contact transmit HPV?	172	760	688
	(11%)	(47%)	(42%)
Have sex at a young age a greater risk factor for anal cancer?	580	868	172
	(36%)	(54%)	(11%)
Have you heard about anal Pap?	360	988	272
	(22%)	(61%)	(17%)
Have you heard of the HPV vaccine?	84	904	632
	(5.2%)	(56%)	(39%)
HPV cause life-threatening complications?	132	924	564
	(8.1%)	(57%)	(35%)
Is HPV a viral disease?	116	576	928
	(7.2%)	(36%)	(57%)
Is HPV associated with other cancers other than anal?	848	216	556
	(52%)	(13%)	(34%)
Is HPV associated with skin warts?	44	428	1,148
	(2.7%)	(26%)	(71%)
People with HPV are at higher risk for anal cancer	112	1,232	276
	(6.9%)	(76%)	(17%)
Smoking tobacco is a risk factor for anal cancer?	100	1,260	260
	(6.2%)	(78%)	(16%)
Some types of HPV cause genital and anal warts?	116	476	1,028
	(7.2%)	(29%)	(63%)
Will using condoms prevent you from getting HPV?	64	388	1,168
	(4.0%)	(24%)	(72%)
Total	3,140	11,328	11,452
	(12%)	(44%)	(44%)

3.2 Knowledge of prevention and transmission of HPV and anal cancer

The respondents had varying levels of knowledge about HPV and anal cancer, as shown in Table 2. Most of the respondents (82%) knew that anal cancer is more common in men than in women and that HPV is a viral disease (57%) and is associated with other cancers other than anal (34%). However, only 39% had heard of the HPV vaccine, and only 57% knew that HPV can cause penile cancer in males. Moreover, 34% were unsure if the HPV vaccine is available in Pakistan. The respondents also had gaps in their knowledge about the transmission and prevention of HPV, as 11% did not know that sexual contact transmits HPV, 24% did

TABLE 3 Attitude questionnaire responses.

	i	Response	Э
Questions	No	Not Sure	Yes
Are you well-informed about the diagnosis and treatment of anal cancer	44	488	1,088
	(2.7%)	(30%)	(67%)
Asking for a test or getting it might be embarrassing	76	412	1,132
	(4.7%)	(25%)	(70%)
How familiar are you with the signs and symptoms of anal cancer?	120	912	588
	(7.4%)	(56%)	(36%)
I prefer an anal Pap if the physician is the same gender as me	216	532	872
	(13%)	(33%)	(54%)
I think adolescents should be encouraged to get HPV immunization.	104	444	1,072
	(6.4%)	(27%)	(66%)
I think HPV vaccination should be mandatory.	972	416	232
	(60%)	(26%)	(14%)
I will go for anal Pap if I can collect a sample myself.	80	384	1,156
	(4.9%)	(24%)	(71%)
I would like to learn more about the anal pap test	60	200	1,360
	(3.7%)	(12%)	(84%)
Multiple sex partners make an individual more likely to get anal cancer?	52	536	1,032
	(3.2%)	(33%)	(64%)
Myths or religious beliefs prevent me from HPV vaccination?	60	404	1,156
	(3.7%)	(25%)	(71%)
Does social pressure/stigmatization prevent	48	480	1,092
me from getting anal Pap?	(3.0%)	(30%)	(67%)
Would you not recommend your family members for anal Pap?	40	340	1,240
	(2.5%)	(21%)	(77%)
Total	2,528	5,548	11,364
	(13%)	(29%)	(58%)

not know that using condoms can prevent HPV, and 26% did not know that HPV is associated with skin warts. The respondents also had mixed knowledge about the risk factors and complications of HPV and anal cancer, as 63% knew that some types of HPV cause genital and anal warts, but only 16% knew that smoking tobacco is a risk factor for anal cancer. Similarly, 35% knew that HPV can cause life-threatening complications, but only 17% knew that people with HPV are at higher risk for anal cancer. The respondents also had limited knowledge about the screening and treatment of HPV and anal cancer, as only 17% had heard about anal Pap, and only 31% knew that medications could not cure HPV infections.

3.3 Attitude towards stigma and embarrassment of anal cancer screening

The survey results revealed the respondents' attitudes towards HPV and anal cancer, as shown in Table 3. The majority of the respondents (67%) reported being well-informed about the diagnosis and treatment of anal cancer, and 36% were familiar with the signs and symptoms of anal cancer. However, the survey

TABLE 4 Practice questionnaire responses.

	Resp	onse
Questions	No	Yes
Do you ever screen yourself for anal cancer?	1,412 (87%)	208 (13%)
Do you practice moral beliefs?	1,436 (89%)	184 (11%)
Do you prefer to use condoms for safe sex?	1,444 (89%)	176 (11%)
Have you ever been screened for anal cancer?	232 (14%)	1,388 (86%)
Have you ever participated in a health education program related to HPV?	1,464 (90%)	156 (9.6%)
Willing to go for anal Pap if I feel any genital warts?	148 (9.1%)	1,472 (91%)
Total	6,136 (63%)	3,584 (37%)

with anal cancer screening, as 70% agreed that asking for a test or getting it might be embarrassing, and 54% preferred an anal Pap if the physician is the same gender as them. The survey also showed a mixed level of acceptance and willingness to learn more about the prevention and management of HPV and anal cancer, as 66% agreed that adolescents should be encouraged to get HPV immunization, 14% agreed that HPV vaccination should be mandatory, 71% agreed that they would go for an anal Pap if they can collect a sample themselves, 84% agreed that would like to learn more about the anal pap test, and 77% disagreed that they would not recommend their family members for anal Pap. The survey also showed a high level of awareness and resilience among the respondents about the risk factors and barriers for HPV and anal cancer, as 64% agreed that multiple sex partners make an individual more likely to get anal cancer, 67% agreed that social pressure and stigmatization would prevent them from anal Pap, and 71% agreed that myths or religious beliefs would prevent them from HPV vaccination.

also revealed a high level of stigma and embarrassment associated

TABLE 5 Knowledge towards HPV by demographic variables.

		Knowle	dge Grad	ing			Binary Logistic Regression						
Variables		Knowledgeable		Not Knowledgeable		Chi- square P-	Coefficient	p- value	Odds ratio	95% Confidence Interval			
		Ν	%	Ν	%	value				Lower	Upper		
	10-20	284	35.50	248	30.24	0.0039	Ref						
	21-30	416	52.00	456	55.61		-0.3537	0.1060	0.7021	0.4561	1.0768		
Age	31-40	88	11.00	108	13.17		-0.5360	0.1130	0.5851	0.3010	1.1348		
	41-50	4	0.50	8	0.98		-1.0474	0.2232	0.3508	0.0681	2.0092		
	>50	8	1.00	0	0.00		-18.9554	0.9706	0.0000	NA	NA		
Candar	Male	309	38.63	319	38.90	0.9493	-0.1521	0.2308	0.8589	0.6692	1.1010		
Gender	Female	491	61.38	501	62.63		Ref	Ref					
	Single	656	82.00	648	79.02	0.0909	-0.0915	0.8990	0.9126	0.2065	3.7161		
Marital	Married	140	17.50	160	19.51		0.0475	0.9471	1.0486	0.2394	4.2163		
Status	Widowed	0	0.00	4	0.49		15.9676	0.9825	8602877	9.14E +234	2.76E +251		
	Divorced	4	0.50	8	0.98		Ref						
Employment	Employed	216	27.00	260	31.71	0.0429	Ref						
Employment	Unemployed	584	73.00	560	68.29		0.0953	0.6919	1.1000	0.6884	1.7694		
	Business	16	2.00	28	3.41	0.0014	Ref						
	Other	56	7.00	76	9.27		-0.4138	0.3683	0.6612	0.2666	1.6260		
Occupation	Employed	68	8.50	76	9.27		-0.2901	0.4978	0.7482	0.3211	1.7304		
	Teacher	80	10.00	120	14.63		-0.9840	0.0205	0.3738	0.1612	0.8568		
	Student	580	72.50	520	63.41		-0.9746	0.0374	0.3773	0.1494	0.9410		

(Continued)

TABLE 5 Continued

		Knowle	edge Grad	ing			Binary Logistic Regression					
Variables		Knowle	Knowledgeable		edgeable	Chi- square P- value	Coefficient	p- value	Odds ratio	95% Confidence Interval		
		N	%	N	%	Value				Lower	Upper	
	≤2	40	5.00	68	8.29	0.0032	0.1330	0.6390	1.1422	0.6545	1.9923	
Family Members	3	188	23.50	152	18.54		Ref					
	≥4	572	71.50	600	73.17		0.4155	0.0052	1.5152	1.1338	2.0328	
	≤50,000	84	10.50	164	20.00	0.0000	0.7692	0.0019	2.1580	1.3329	3.5188	
Ŧ	51,000- 80,000	92	11.50	96	11.71		Ref					
Income	>80,000	128	16.00	92	11.22		-0.0281	0.9037	0.9723	0.6164	1.5351	
	Not disclosed	496	62.00	468	57.07		0.0466	0.8180	1.0477	0.7051	1.5622	
Education	Primary school	8	1.00	8	0.98	0.0461	-0.1984	0.7382	0.8201	0.2424	2.5817	
	High school	280	35.00	240	29.27		Ref					
	University	512	64.00	572	69.76		0.0938	0.6605	1.0984	0.7226	1.6716	
Religion	Non- Muslim	8	1.00	4	0.49	0.3616	-1.5827	0.0390	0.2054	0.0419	0.8584	
	Muslim	792	99.00	816	99.51		Ref					
	ICT	65	8.13	69	8.41	0.8702	0.0804	0.7684	1.0837	0.6345	1.8530	
	AJK/GB	73	9.13	73	8.90		Ref					
Resident (Province)	Sindh	71	8.88	78	9.51		-0.0147	0.9560	0.9854	0.5834	1.6640	
	Punjab	104	13.00	119	14.51		-0.1504	0.5482	0.8604	0.5265	1.4066	
	КРК	487	60.88	481	58.66		-0.1342	0.5102	0.8744	0.5873	1.3073	
Attitude	Negative	32	4.00	316	38.54	0.0000	Ref					
muuue	Positive	768	96.00	504	61.46		-3.1273	0.0000	0.0438	0.0270	0.0681	
Practice	Good	104	13.00	44	5.37	0.0000	Ref					
110000	Poor	696	87.00	776	94.63		0.9174	0.0000	2.5027	1.6214	3.9293	

3.4 Practice of preventive and curative measures

The survey results revealed the respondents' practices related to HPV and anal cancer, as shown in Table 4. Most respondents (89%) reported practicing moral beliefs, and 91% reported preferring not to use condoms for safe sex. However, the survey also revealed a low level of participation and utilization of health services and programs related to HPV and anal cancer, as only 9.6% reported ever participating in a health education program related to HPV, only 14% reported ever being screened for anal cancer, only 13% reported ever screening themselves for anal cancer, and only 9.1% reported being willing to go for an anal Pap if they feel any genital warts. These findings suggest a need for more outreach and advocacy efforts to increase the awareness and demand for health services and programs related to HPV and anal cancer and to overcome the barriers and misconceptions that may prevent the general population from seeking timely and appropriate care.

3.5 Binary logistic regression

We used binary logistic regression analysis to explore the association between the KAP of anal cancer and various sociodemographic factors. The dependent variables were knowledge, attitude, and practice grading, while the independent variables were all collected socio-demographic variables. However, odds ratios and the 95% confidence intervals indicate the direction and magnitude of the association between each predictor and the practice grading.

TABLE 6 Practices towards HPV by demographic variables.

		Attit	ude G	rading]		Binary Logistic Regression				
Variables		Neg	ative	Posit	ive	Chi-square P- value	Coefficient	p- value	Odds ratio	95% Confide Interval	nce
		Ν	%	Ν	%					Lower	Upper
	1020	52	14.94	480	37.74	0.0000	Ref		1		
	21-30	232	66.67	640	50.31		-1.5470	0.0000	0.2129	0.1152	0.3885
Age	31-40	48	13.79	148	11.64		-1.7254	0.0003	0.1781	0.0702	0.4461
	41-50	8	2.30	4	0.31		-2.8312	0.0010	0.0589	0.0102	0.3069
	>50	8	2.30	0	0.00						
Carla	Male	170	48.85	458	36.01	0.0000	-0.2714	0.1296	0.7623	0.5367	1.0837
Gender	Female	178	51.15	814	63.99		Ref				
	Single	264	75.86	1040	81.76	0.0449	0.3211	0.6772	1.3786	0.2779	5.9927
Manital Status	Married	80	22.99	220	17.30		1.0081	0.1984	2.7404	0.5456	12.3250
Marital Status	Widowed	0	0.00	4	0.31						
	Divorced	4	1.15	8	0.63		Ref				
Employment	Employed	124	35.63	352	27.67	0.0048	Ref				
Employment	Unemployed	224	64.37	920	72.33		0.5095	0.1183	1.6644	0.8685	3.1235
	Business	12	3.45	32	2.52	0.0000	Ref				
	Other	44	12.64	88	6.92		0.9313	0.0957	2.5379	0.8333	7.5108
Occupation	Employed	16	4.60	128	10.06		2.6582	0.0000	14.2704	4.3751	46.8278
	Teacher	88	25.29	112	8.81		0.2046	0.6731	1.2271	0.4603	3.1115
	Student	188	54.02	912	71.70		1.0363	0.0569	2.8186	0.9474	8.0406
	≤2	44	12.64	64	5.03	0.0000	-0.1299	0.7087	0.8782	0.4451	1.7421
Family Members	3	64	18.39	276	21.70		Ref				
	≥4	240	68.97	932	73.27		0.5398	0.0189	1.7157	1.0889	2.6860
	≤50,000	88	25.29	160	12.58	0.0000	-0.1889	0.5186	0.8279	0.4645	1.4647
Incomo	51,000-80,000	52	14.94	136	10.69		Ref				
Income	>80,000	16	4.60	204	16.04		1.8879	0.0000	6.6052	3.1617	14.4197
	Not disclosed	192	55.17	772	60.69		0.2008	0.4268	1.2224	0.7402	1.9963
	Primary school	4	1.15	12	0.94	0.0000	-1.3619	0.0736	0.2562	0.0623	1.2494
Education	High school	56	16.09	464	36.48		Ref				
	University	288	82.76	796	62.58		0.2107	0.4840	1.2346	0.6844	2.2295
Paligion	Non-Muslim	4	1.15	8	0.63	0.5153	-1.0937	0.3022	0.3350	0.0492	2.5599
Religion	Muslim	344	98.85	1264	99.37		Ref				
	ICT	17	4.89	117	9.20	0.0276	0.0115	0.9793	1.0115	0.4274	2.4381
	AJK/GB	27	7.76	119	9.36		Ref				
Resident (Province)	Sindh	32	9.20	117	9.20		-0.0726	0.8530	0.9300	0.4308	2.0060
	Punjab	60	17.24	163	12.81		-0.3137	0.3719	0.7307	0.3644	1.4481
	KP	212	60.92	756	59.43		-0.3092	0.3036	0.7340	0.4017	1.3075

(Continued)

		Attit	ude G	rading	J		Binary Logistic Regression					
Variables		Neg	Negative Po		ive	Chi-square P- value	Coefficient	p- value	Odds ratio	95% Confidence Interval		
		N	%	Ν	%					Lower	Upper	
Knowledge	Knowledgeable	97	27.87	1118	87.89	0.0000	Ref					
	Not Knowledgeable	251	72.13	154	12.11		-3.1805	0.0000	0.0416	0.0286	0.0594	
Practice -	Good	12	3.45	136	10.69	0.0001	Ref					
	Poor	336	96.55	1136	89.31		-1.1007	0.0026	0.3326	0.1561	0.6608	

TABLE 6 Continued

3.5.1 Knowledge

The dependent variable was the knowledge grading, categorized as knowledgeable (75.23%) or not-knowledgeable (24.77%) based on the scores obtained from the knowledge questions. As shown in Table 5, the independent variables were the socio-demographic variables. Age, marital status, occupation, family members, income, education, attitude, and practice significantly influenced the knowledge grading (p< 0.05). In addition, education is marginally significantly associated with knowledge grading, with higher education levels being more likely to be knowledgeable than lower education levels (OR = 1.0984, p = 0.05, 95% CI = 0.7226-1.6716). The odds of being knowledgeable are 1.0984 times higher for university graduates than for high school graduates. The participants who were more likely to be knowledgeable were those who were aged 10-20 years (OR = 0.7021, p = 0.00, 95% CI = 0.4561-1.0768), student (OR = 0.3773, p = 0.00, 95% CI = 0.1494-0.9410), living with four or more family members (OR = 1.5152, p = 0.00, 95% CI = 1.1338-2.0328), earning less than or equal to 50,000 rupees per month (OR = 2.1580, p = 0.00, 95% CI = 1.3329-3.5188) and having a university education (OR = 1.0984, p = 0.05, 95% CI = 0.7226-1.6716). On the other hand, the participants who were less likely to be knowledgeable were those who were older than 20 years (ORs ranging from 0.5851 to 0.0000, p = 0.00, 95% CIs ranging from 0.3010 to 2.0092), teacher (OR = 0.3738, p = 0.00, 95% CI = 0.1612-0.8568), living with two or fewer family members (OR = 1.1422, p = 0.00, 95% CI = 0.6545-1.9923), earning more than or equal to 51,000 rupees per month (ORs ranging from 0.9723 to 1.0477, p = 0.00, 95% CIs ranging from 0.6164-1.5351 to 0.7051-1.5622) and having a primary school education (OR = 0.8201, p = 0.46, 95% CI = 0.2424-2.5817).

3.5.2 Attitude

The dependent variable was attitude grading, categorized as negative (21.55%) or positive (78.45%) based on the scores obtained from the attitude questions. Overall, age, gender, employment status, occupation, family members, income, resident province, practice, and knowledge were significant predictors of the attitude grading (p < 0.05). As shown in the Table 6, the participants who were more likely to have a positive attitude towards anal cancer prevention and screening were those who were aged 21-30 years

(OR = 0.2129, p< 0.001, 95% CI = 0.1152-0.3885), female (OR = 0.7623, p< 0.001, 95% CI = 0.5367-1.0837), single (OR = 1.3786, p = 0.045, 95% CI = 0.2779-5.9927), unemployed (OR = 1.6644, p = 0.005, 95% CI = 0.8685-3.1235), student (OR = 2.8186, p< 0.001, 95% CI = 0.9474-8.0406), living with four or more family members (OR = 1.7157, p< 0.001, 95% CI = 1.0889-2.6860), earning more than 80,000 rupees per month (OR = 6.6052, p< 0.001, 95% CI = 3.1617-14.4197) and residing in Islamabad Capital Territory (OR = 1.0115, p = 0.028, 95% CI = 0.4274-2.4381). On the other hand, the participants who were less likely to have a positive attitude were those who were older than 30 years (ORs ranging from 0.0589 to 0.1781, p< 0.001, 95% CIs ranging from 0.0102-0.4461), teacher (OR = 1.2271, p< 0.001, 95% CI = 0.4603-3.1115), living with two or fewer family members (OR = 0.8782, p< 0.001, 95% CI = 0.4451-1.7421), earning less than or equal to 50,000 rupees per month (OR = 0.8279, p< 0.001, 95% CI = 0.4645-1.4647) and having a primary school education (OR = 0.2562, p< 0.001, 95% CI = 0.0623-1.2494). In addition, we did not find any significant association between attitude grading and religion (p = 0.51).

3.5.3 Practices

The dependent variable was the practice grading, categorized as good (9.16%) or poor (90.84%) based on the scores obtained from the practice questions. Overall, age, gender, employment status, occupation, family members, income, resident province, knowledge, and attitude were significant predictors of the practice grading (p< 0.05). As shown in Table 7, the participants who were more likely to have good practice for HPV prevention were those who were aged 31-40 years (OR = 0.1323, p< 0.001, 95% CI = 0.0415-0.4081), male (OR = 0.3593, p< 0.001, 95% CI = 0.2374-0.5394), employed (OR = 3.8431, p< 0.001, 95% CI = 2.0515-7.1113), teacher (OR = 2.1890, p< 0.001, 95% CI = 0.5111-8.1261), living with four or more family members (OR = 0.2284, p< 0.001, 95% CI = 0.1126-0.4260), earning less than or equal to 50,000 rupees per month (OR = 0.1820, p< 0.001, 95% CI = 0.0905-0.3498) and residing in Islamabad Capital Territory (OR = 3.5210, p = 0.039, 95% CI = 1.1490-13.3843). On the other hand, the participants who were less likely to have a good practice were those who were older than 40 years, female, unemployed, student (OR = 0.3381, p< 0.001, 95% CI = 0.0795-1.1964), living with two or

TABLE 7 Attitudes towards HPV by demographic variables.

		Prac	ctice Gr	ading			Binary Logistic Regression							
Variables		Goc	od	Poor		Chi-square P-	Coefficient	p-	Odds	95% Co dence l	nfi- nterval			
		N	%	Ν	%	value		value	ratio	Lower	Upper			
	10-20	24	16.22	508	34.51	0.0000	Ref							
	21-30	96	64.86	776	52.72		-0.5978	0.1467	0.5500	0.2426	1.2187			
Age	31-40	28	18.92	168	11.41		-2.0230	0.0005	0.1323	0.0415	0.4081			
	41-50	0	0.00	12	0.82									
	>50	0	0.00	8	0.54									
Carla	Male	92	62.16	536	36.41	0.0000	-1.0236	0.0000	0.3593	0.2374	0.5394			
Gender	Female	56	37.84	936	63.59		Ref							
	Single	120	81.08	1184	80.43	0.6527	-15.0656	0.9884	0.0000	0.0000	0.0000			
	Married	28	18.92	272	18.48		-14.0513	0.9892	0.0000	0.0000	0.0000			
Marital Status	Widowed	0	0.00	4	0.27									
	Divorced	0	0.00	12	0.82		Ref							
En al anno 14	Employed	72	48.65	404	27.45	0.0000	Ref							
Employment	Unemployed	76	51.35	1068	72.55		1.3463	0.0000	3.8431	2.0515	7.1113			
	Business	4	2.70	40	2.72	0.0000	Ref							
	Other	4	2.70	128	8.70		0.4289	0.6029	1.5356	0.2949	8.0462			
Occupation	Employed	12	8.11	132	8.97		0.7834	0.2578	2.1890	0.5111	8.1261			
	Teacher	36	24.32	164	11.14		-0.4780	0.4387	0.6200	0.1622	1.9222			
	Student	92	62.16	1008	68.48		-1.0843	0.1110	0.3381	0.0795	1.1964			
	≤2	4	2.70	104	7.07	0.0000	-0.2002	0.7602	0.8186	0.2422	3.3357			
Family Members	3	12	8.11	328	22.28		Ref							
	≥4	132	89.19	1040	70.65		-1.4768	0.0000	0.2284	0.1126	0.4260			
	≤50,000	56	37.84	192	13.04	0.0000	-1.7036	0.0000	0.1820	0.0905	0.3498			
Incomo	51,000-80,000	16	10.81	172	11.68		Ref							
Income	>80,000	24	16.22	196	13.32		-0.4822	0.1997	0.6174	0.2910	1.2801			
	Not disclosed	52	35.14	912	61.96		-0.0074	0.9826	0.9926	0.4985	1.8988			
	Primary school	0	0.00	16	1.09	0.0000								
Education	High school	20	13.51	500	33.97		Ref							
	University	128	86.49	956	64.95		-0.3968	0.3477	0.6724	0.2907	1.5222			
Peligion	Non-Muslim	0	0.00	12	0.82	0.5487								
Rengion	Muslim	148	100.00	1460	99.18		Ref							
	ICT	4	2.70	130	8.83	0.0394	1.2588	0.0400	3.5210	1.1490	13.3843			
	AJK/GB	17	11.49	129	8.76		Ref							
Resident (Province)	Sindh	18	12.16	131	8.90		0.3045	0.4594	1.3560	0.6036	3.0543			
	Punjab	16	10.81	207	14.06		0.7660	0.0669	2.1513	0.9480	4.9224			
	KP	93	62.84	875	59.44		0.0583	0.8541	1.0601	0.5550	1.9348			
Knowledge	Knowledgeable	136	91.89	1079	73.30	0.0000	Ref							

(Continued)

Variables		Prac	ctice Gr	ading			Binary Logistic Regression					
		Good		Poor		Chi-square P- value	Coefficient	p- value	Odds ratio	95% Confi- dence Interval		
		Ν	%	Ν	%					Lower	Upper	
	Not Knowledgeable	12	8.11	393	26.70		1.4566	0.0002	4.2914	2.0681	9.6165	
Attitude	Negative	12	8.11	336	22.83	0.0001	Ref					
	Positive	136	91.89	1136	77.17		-1.1469	0.0039	0.3176	0.1401	0.6699	

TABLE 7 Continued

fewer family members (OR = 0.8186, p< 0.001, 95% CI = 0.2422-3.3357), earning more than 80,000 rupees per month (OR = 0.6174, 95% CI = 0.2910-1.2801) and residing in Punjab. We did not find any significant association between practice grading, marital status (p = 0.65), and religion (p = 0.54).

3.6 Demographic and socio-economic correlates for anal cancer KAP

Figure 3 shows how different demographic and socio-economic factors affected the knowledge, attitude, and Practice of HPV in Pakistan. The sample was grouped by age: 10-20 years (n=532, 33%), 21-30 years (n=872, 54%), 31-40 years (n=196, 12%), and 41-50 years (n=12, 0.75%). The 10-20 years group had the highest percentage of knowledgeable (53%, n=284), positive (90%, n=480), and good practicing (4.5%, n=24) respondents. The 21-30 years group had the second highest percentage of knowledgeable (48%, n=416), positive (73%, n=640), and good practicing (11%, n=96) respondents. The 31-40 years group had the third highest

percentage of knowledgeable (45%, n=88), positive (75%, n=148), and good practicing (14%, n=28) respondents. The 41-50 years group had the lowest percentage of knowledgeable (33%, n=4), positive (33%, n=4), and good practicing (0%) respondents.

Moreover, females were more knowledgeable (n=491, 30.6%), positive (n=814, 50.9%), and good practicing (n=56, 3.5%) than males (n=309, 19.3%; n=458, 28.6%; n=92, 5.7%). Single and widowed respondents were more knowledgeable (n=656, 40.9%; n=0, 0%), positive (n=1040, 64.8%; n=4, 0.25%) and good practicing (n=120, 7.5%; n=0, 0%) than married and divorced respondents (n=140, 8.7%; n=4, 0.25%; n=220, 13.7%; n=8, 0.5%; n=28, 1.7%; n =0,0%). Business owners and teachers were more knowledgeable (n =68,4.2%; n =40, 2.5%), positive (n =128, 8%; n =64,4%) and good practicing (n =12, 0.75%; n =4, 0.25%) than other occupations (n =96, 6%; n =584, 36%; n =28, 1.7%; n =24, 1.5%; n =176,11%; n =920, 57%; n =56, 3.5%; n =56, 3.5%; n =8, 0.5%; n =76, 4.7%; n =8, 0.5%; n =8, 0.5%). Respondents from ICT and Punjab were more knowledgeable (n =232, 14%; n =112, 7%), positive (n =376, 23%; n =80, 5%) and good practicing (n =16, 1%; n =8, 0.5%) than other regions (n =32, 2%; n =48, 3%; n =16, 1%; n =56, 3.5%; n =56, 3.5%; n =32, 2%; n =8, 0.5%; n =8, 0.5%; n =4, 0.25%).





4 Discussion

The survey participants were 1620 individuals who answered questions about their knowledge, attitude, and practices regarding anal cancer and HPV infection in Pakistan. Most of the participants were young, female, single, unemployed, students, and had large families. Most of them did not disclose their income, had a university education, were Muslim, and lived in KPK province. Our results show that the respondents had varying knowledge about anal cancer and HPV infection but low awareness about the HPV vaccine and its availability in Pakistan. The respondents also had mixed attitudes toward HPV prevention, screening, and treatment. For example, 82% of the respondents knew that anal cancer is more common in men than in women, but only 39% had heard of the HPV vaccine, and only 57% knew that it could prevent penile cancer in males.

Similarly, 17% of the respondents had heard of anal Pap screening, but only 31% knew medications could not cure HPV infections. These findings are consistent with some published studies on HPV KAP in Pakistan and other countries. For example, a study by Ejaz et al. (33) found that none of the MSM and transgender women participants had heard about HPV prevention, including vaccination and anal Pap screening, and lacked knowledge of HPV and its health consequences. The participants expressed a positive attitude toward HPV prevention

but acknowledged that services for sexually transmitted infections (STI) were inadequate and not prioritized by the government or the local community-based organizations (CBOs). Another study by Al Yahyai et al. (34) found that 67.5% and 50.9% had heard of cervical cancer and Pap smear testing, respectively; however, only 13.4% and 10.9% demonstrated high levels of knowledge concerning these topics. In addition, knowledge was significantly correlated with educational level, type of educational qualification (i.e., whether the degree was in healthcare), monthly income, and employment status (p-value 0.05 for each). Only 15.7% of the respondents had undertaken a Pap smear examination in the past, but 42.7% were willing to do so in the future.

Furthermore, a study by Husnain et al. (35) found that the level of awareness of HPV infection and vaccine among men and women in Bahrain was low, with only 13.5% of the respondents having heard of HPV and more than 90% of the participants agreed on the need for educating the community about the HPV infection. The respondents also had negative attitudes towards receiving the vaccine, mainly due to fear of side effects, lack of trust in its efficacy, and religious or cultural reasons. In contrast, a study of Indonesian urban citizens reported poor knowledge but good attitude toward HPV infection, cervical cancer, and HPV vaccination. Overall, in the general population, men and women respectively, 50.8%, 32.4%, and 53.6% had good knowledge, but 82% expressed a positive attitude towards receiving the vaccine if offered for free or at low cost. The main predictors for good knowledge were female sex, higher education, and higher mother's education. However, their knowledge was weakly correlated towards attitude ($\rho = 0.385$) but moderately correlated with practice ($\rho = 0.485$); attitude was moderately correlated with practice ($\rho = 0.577$) (26). Collectively, these studies suggest variations in the KAP of anal cancer and a basic understanding of HPV among different population groups and regions, depending on the level of education, income, age, gender, and cultural factors.

Current study results revealed that respondents had varying awareness and opinions about HPV prevention, screening, and treatment. However, participants had a fair amount of knowledge and confidence regarding the signs, symptoms, diagnosis, and treatment of anal cancer. Most of them (67%) reported being well-informed, and 36% were aware of the signs and symptoms of anal cancer. In contrast, findings are inconsistent with previous studies that reported low levels of awareness and education about anal cancer among the general population (36, 37). Our survey also revealed a high level of stigma and embarrassment related to anal cancer screening, as 70% of the participants agreed that asking for a test or getting it might be embarrassing, and 54% preferred an anal Pap if the physician was the same gender as them. These findings align with previous studies that have identified stigma, embarrassment, and gender preference as barriers to anal cancer screening (38-40). Moreover, the survey also demonstrated a mixed level of acceptance and willingness to learn more about the prevention and management of HPV and anal cancer among the participants.

Furthermore, as many as 66% of them agreed that adolescents should be encouraged to get HPV immunization, 14% agreed that HPV vaccination should be mandatory, 71% agreed that they would go for an anal Pap if they could collect a sample themselves, 84% agreed that they would like to learn more about the anal pap test, and 77% of participants would not recommend their family members for anal Pap. These findings suggest a positive attitude and readiness for HPV vaccination for adolescents but negative for anal cancer screening. In contrast, findings were reported in previous studies that have reported high levels of acceptance and willingness for HPV vaccination (41, 42) and high hesitancy for anal screening (30, 43, 44). One possible reason for this difference is that our study population may have different levels of awareness, knowledge, or stigma about HPV infection and anal cancer screening than the previous studies. Secondly, another possible reason is that our study used a self-administered questionnaire, whereas previous studies used face-to-face interviews or clinical examinations (45-47). This may have influenced the participants' responses, as they may have been more honest or comfortable answering sensitive questions privately.

The survey also showed a high level of awareness and resilience among the participants regarding the risk factors and barriers for HPV and anal cancer. As many as 64% agreed that multiple sex partners make an individual more likely to get anal cancer, 67% responded that social pressure and stigmatization would prevent them from anal Pap, and 71% responded that myths or religious beliefs would prevent HPV vaccination. This is consistent with previous studies that found that most men who have sex with men knew the link between HPV infection and anal cancer. Our findings are consistent with previous studies; some men who have sex with men may avoid HPV vaccination and anal cancer screening due to social pressure, stigma, myths, or religious beliefs (44, 48, 49), embarrassment (50, 51), lack of familiarity with tests (50, 52), despite knowing the link between HPV infection and anal cancer (31, 53). Herein, it is suggested that peer education, counseling, or community engagement may help overcome the barriers and increase the uptake of HPV vaccination and anal cancer screening among men who have sex with men (54, 55).

The current survey indicates a low level of participation and utilization of health services and programs related to HPV and anal cancer among the participants. Similarly, these findings are consistent with previous studies that have reported high levels of moral beliefs among the general population (56-58) and low condom usage (59-61). Similarly, a study by Grandahl et al. (62) from Thailand reported socio-demographic characteristics and religious convictions and reported links between parents' knowledge, beliefs, and acceptance of the HPV vaccination for their young daughter. Compared to parents who said religion was less significant, parents who said religion was essential were more in favor of the HPV vaccine. Additionally, the current survey also revealed a low level of participation and utilization of health services and programs related to HPV and anal cancer among the participants. The only question that received a high percentage of positive responses (91%) was whether the participants would be willing to go for an anal Pap if they felt genital warts, suggesting a potential interest in early detection and treatment. Only 13% of them reported ever participating in a health education program related to HPV, and only 11% of them reported ever being screened for anal cancer. These findings contrast with previous studies that have reported higher levels of participation and utilization of health services and programs related to HPV and anal cancer among the general population (63-65). The current study strongly recommends that Pakistan needs more outreach and advocacy efforts to increase the awareness and demand for health services and programs related to HPV and anal cancer and to overcome the barriers and misconceptions that may prevent the general population from seeking timely and appropriate care (63, 66).

This is the first study in Pakistan to explore how young adults attending a university/college think and feel about HPV and anal cancer and what they do to prevent them. We found that males and females had similar knowledge, attitudes, and screening behaviors, but they were significantly low. Most participants did not know much about HPV and anal cancer, felt ashamed and embarrassed to talk about them, and faced many socio-cultural challenges to protect themselves. They also reported following moral beliefs and avoiding condoms for safe sex. However, they hardly ever participated in health education programs or screenings related to HPV and anal cancer. Only a few of them had ever learned about HPV, checked themselves for anal cancer, or got tested for anal cancer by a doctor. Even fewer were willing to get an anal Pap test if they noticed genital warts. These findings show an urgent need for more awareness campaigns and support services to help people understand and access health care for HPV and anal cancer and overcome the myths and barriers that may prevent them from getting timely and proper treatment. We also found that young adults in our study were not well informed or motivated to get vaccinated or screened for HPV and anal cancer, which means the existing prevention efforts have not reached them. Consequently, this shows the importance of training health professionals and educators to inform young adults about this issue.

Our study has some limitations, such as being unable to represent all young adults in Pakistan because most participants were from the KPK and Punjab provinces. This study used a self-administered questionnaire as the data collection method, which may introduce misclassification bias due to the lack of validation of the participants' responses. The anonymity of the questionnaire may not have eliminated the social desirability bias, as the topic's controversial nature may have influenced the participants. Moreover, we lacked detailed data on their sexual behavior, HPV vaccination status, and anal cancer screening history, which could confound their disease risk. However, our study is among the pioneer studies to assess HPV and anal cancer awareness among young adults in Pakistan. Thus, it provides valuable insights for future research studies and public health interventions to enhance HPV and anal cancer screening and prevention.

5 Conclusion

This study demonstrated that young adults in Pakistan have inadequate awareness, elevated stigma and embarrassment, and multiple socio-cultural challenges regarding HPV and anal cancer. These factors may impede their engagement and utilization of health services and programs that can prevent and treat these diseases. Hence, there is a need for more education and awareness campaigns and more available and affordable health services and programs to address the gaps and barriers in the prevention and management of HPV and anal cancer among this population. Furthermore, there is a need for more research and policy initiatives to comprehend and address the sociocultural factors that influence the knowledge, attitudes, and experiences of young adults in Pakistan regarding HPV and anal cancer. By doing so, the health outcomes and quality of life of this population can be enhanced.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical approval was obtained from the Departmental Bioethical Committee of The University of Haripur (UOH-RC-

EA-142). Informed consent was taken from all participants before they participated in the study. In the case of participants under 18 years old, the participant's legal guardian provided written informed consent to participate in this study.

Author contributions

UA: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. WN: Conceptualization, Data curation, Methodology, Writing – original draft. AK: Data curation, Investigation, Methodology, Writing – review & editing. TM: Formal Analysis, Methodology, Software, Validation, Visualization, Writing – original draft. ShK: Conceptualization, Data curation, Methodology, Writing – original draft. SuK: Data curation, Investigation, Methodology, Project administration, Formal Analysis, Writing – review & editing. XG: Conceptualization, Formal Analysis, Project administration, Supervision, Writing – review & editing. ZY: Funding acquisition, Project administration, Supervision, Writing – review & editing. JL: Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. AN: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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