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Original Article

Variants Specific Clinical Characteristics of SARS-CoV-2: A Cross-Sectional Study in Khyber Pakhtunkhwa, Pakistan

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ABSTRACT

Background: SARS-CoV-2 has evolved into multiple variants with potential differences in transmissibility, pathogenicity, and clinical presentation. Understanding variant-specific symptom profiles is essential for improving surveillance, diagnosis, and clinical management, particularly in resource-limited settings where genomic sequencing is limited. Objective: To compare the clinical characteristics associated with Alpha, Beta, Gamma, and Delta SARS-CoV-2 variants among PCR-confirmed COVID-19 cases in Khyber Pakhtunkhwa, Pakistan. Methods: A cross-sectional observational study was conducted at the Public Health Reference Laboratory, Khyber Medical University, using PCR-confirmed COVID-19 cases recorded between 2020 and 2023. SARS-CoV-2 variants were identified using mutation-specific PCR assays. Clinical and demographic data were collected through structured telephone interviews based on the World Health Organization COVID-19 case report form. Descriptive statistics and inferential analyses including chi-square and Fisher–Freeman–Halton tests were performed using SPSS version 25, with statistical significance set at $p<0.05$. Results: Among 416 participants, the Delta variant accounted for the majority of infections (310; 74.5%), followed by Gamma (60; 14.4%), Alpha (36; 8.7%), and Beta (10; 2.4%). Delta infections were strongly associated with fever, cough, sore throat, body aches, and loss of smell and taste, each exceeding 94% prevalence. Gamma infections demonstrated high rates of fatigue, rigors, chills, rhinorrhea, and shortness of breath (>90%), whereas Beta infections showed prominent gastrointestinal symptoms including nausea and vomiting (70%). Alpha infections had the highest proportion of asymptomatic cases (27.8%). Conclusion: SARS-CoV-2 variants exhibited distinct clinical phenotypes in this population, with Delta characterized by respiratory and sensory symptoms, Gamma by systemic inflammatory manifestations, and Beta by gastrointestinal involvement. Recognition of variant-specific symptom clusters may support improved clinical detection and epidemiological surveillance in settings with limited genomic sequencing capacity. Keywords: SARS-CoV-2, COVID-19, clinical characteristics, variants, Delta variant, Pakistan.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19), has caused one of the most significant global public health crises since the 1918 influenza pandemic. Since its emergence in Wuhan, China, in late 2019, the virus has spread rapidly across continents, resulting in millions of deaths and profound social, economic, and healthcare disruptions worldwide (1). Transmission occurs primarily through respiratory droplets and close contact with infected individuals, although indirect transmission through contaminated surfaces has also been documented (5,6). In response to the rapidly evolving situation, the World Health Organization declared COVID-19 a Public Health Emergency of International Concern on 30 January 2020, followed by its

classification as a global pandemic shortly thereafter (1,3). Although the global emergency phase ended in 2023, SARS-CoV-2 continues to circulate and evolve, emphasizing the importance of ongoing epidemiological and clinical characterization of emerging viral variants.

A defining feature of SARS-CoV-2 epidemiology has been the emergence of genetically distinct variants resulting from viral mutations that alter transmissibility, immune escape potential, and possibly clinical manifestations. Several variants have been classified as variants of concern due to their increased transmissibility or potential impact on disease severity and public health responses. Among the earliest widely circulating variants were Alpha (B.1.1.7), first identified in the United Kingdom in 2020; Beta (B.1.351), detected in South Africa; Gamma (P.1), identified in Brazil; and Delta (B.1.617.2), first reported in India in 2021 (9). These variants exhibited differences in viral transmissibility and epidemiological patterns, with the Delta variant in particular demonstrating substantially higher transmissibility and rapidly becoming the dominant strain in many regions before the emergence of later variants. The appearance of multiple variants underscores the adaptive capacity of the virus and highlights the need to understand whether specific variants are associated with distinct clinical presentations or symptom profiles.

Clinical manifestations of COVID-19 vary widely, ranging from asymptomatic infection to severe respiratory failure and multi-organ dysfunction. Most individuals experience mild to moderate disease characterized by symptoms such as fever, dry cough, fatigue, headache, and loss of taste or smell, while a smaller proportion develop severe complications including pneumonia, acute respiratory distress syndrome, and systemic inflammatory responses (10–12). Early epidemiological reports indicated that approximately 80–90% of infections were mild or asymptomatic, whereas severe disease was more likely to occur among older adults or individuals with underlying medical conditions (11,12). However, as new variants emerged, questions arose regarding whether the clinical presentation of COVID-19 remained consistent or differed according to variant type. Understanding potential differences in symptom profiles is important for improving clinical recognition, diagnostic triage, and public health surveillance, particularly in settings where genomic sequencing capacity is limited.

In Pakistan, the first confirmed cases of COVID-19 were reported on 26 February 2020 in Karachi and Islamabad, marking the beginning of a nationwide outbreak that significantly affected the country's healthcare system and population health (13). By 2021, Pakistan had reported hundreds of thousands of confirmed cases and thousands of deaths, reflecting the substantial burden of the pandemic on the country (13). Observational studies conducted within Pakistan have reported common symptoms including fever, dry cough, fatigue, body aches, and loss of smell or taste, with approximately 80% of cases presenting as mild to moderate illness and a smaller proportion progressing to severe disease requiring hospitalization (14,15). The age distribution of cases has also varied widely, although several studies suggest that younger adults represent a substantial proportion of confirmed infections in the country (14). Despite these findings, most available studies in Pakistan have focused on general clinical characteristics of COVID-19 rather than comparing symptom patterns across different SARS-CoV-2 variants.

Globally, several investigations have suggested that certain variants may be associated with variations in symptom prevalence or disease severity. For example, studies conducted during the period of Delta variant predominance reported increased transmissibility and distinct clinical patterns compared with earlier variants (18). Other epidemiological analyses have also indicated shifts in age distribution and infection dynamics associated with variant emergence (19). Nevertheless, evidence regarding variant-specific clinical manifestations remains heterogeneous, and much of the available literature originates from high-income countries with extensive genomic surveillance. In low- and middle-income settings, including Pakistan, limited sequencing capacity and fragmented surveillance systems have restricted the ability to systematically examine variant-related differences in clinical presentation. Consequently,

there is a need for region-specific evidence to better understand how different SARS-CoV-2 variants may manifest clinically within local populations.

Khyber Pakhtunkhwa, a major province of Pakistan with diverse geographic and demographic characteristics, experienced multiple waves of COVID-19 during the pandemic period. However, systematic data comparing the clinical characteristics associated with different SARS-CoV-2 variants in this region remain scarce. Identifying whether distinct variants are associated with particular symptom patterns could support improved clinical recognition and inform surveillance strategies, particularly in resource-constrained settings where genomic sequencing may not be routinely available. In such contexts, recognizing variant-related symptom clusters could help clinicians prioritize testing and public health responses during outbreaks.

Therefore, the present study aimed to compare the clinical characteristics of PCR-confirmed SARS-CoV-2 infections attributed to the Alpha, Beta, Gamma, and Delta variants among individuals residing in the seven administrative divisions of Khyber Pakhtunkhwa, Pakistan. Specifically, the study sought to examine differences in symptom prevalence and demographic characteristics across variant groups and to explore the distribution of pre-existing comorbid conditions among infected participants. By addressing this knowledge gap, the study seeks to contribute regional evidence regarding variant-specific clinical presentation of COVID-19 and support ongoing efforts to improve epidemiological understanding and preparedness for future respiratory viral outbreaks.

METHODS

This cross-sectional observational study was conducted to evaluate and compare the clinical characteristics associated with different SARS-CoV-2 variants among laboratory-confirmed COVID-19 cases in Khyber Pakhtunkhwa, Pakistan. The study utilized retrospectively identified PCR-confirmed cases and prospectively collected symptom information through standardized interviews. The research was implemented at the Public Health Reference Laboratory (PHRL), Khyber Medical University (KMU), Peshawar, which serves as a central diagnostic and surveillance facility for COVID-19 testing in the province. Data collection was carried out between July and August 2023, while the underlying PCR-confirmed cases included infections recorded between March 2020 and June 2023 across the seven administrative divisions of Khyber Pakhtunkhwa: Peshawar, Mardan, Malakand, Hazara, Kohat, Bannu, and Dera Ismail Khan. The study design followed internationally recognized reporting standards for observational research and was structured to allow systematic comparison of symptom patterns across SARS-CoV-2 variant groups (29).

Eligible participants were individuals recorded in the PHRL laboratory database with a confirmed SARS-CoV-2 infection based on reverse transcription polymerase chain reaction (RT-PCR) testing during the pandemic period. Individuals were included if they were residents of Khyber Pakhtunkhwa, had a laboratory record of PCR-confirmed infection, and could be contacted for follow-up data collection. Individuals were excluded if the laboratory record lacked sufficient identification information to permit follow-up contact, if PCR confirmation was incomplete or indeterminate, or if the individual declined participation during the follow-up interview. Participant identification numbers and laboratory records were screened to generate a sampling frame of eligible cases. Individuals were subsequently contacted by telephone using the contact details recorded in the laboratory database. During the call, trained research personnel explained the study purpose, procedures, and confidentiality protections before requesting verbal informed consent. Only participants who provided consent were included in the analysis.

Variant identification was performed using archived laboratory data and confirmatory molecular analysis conducted at the PHRL. SARS-CoV-2 variants were determined using the PRIMER DESIGN™ SARS-CoV-2 variant detection PCR kit, which identifies characteristic mutation patterns associated with major variants of concern, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2).

Laboratory procedures were conducted according to the manufacturer's protocol and quality control standards established at the PHRL to ensure assay reliability. Variant classification was recorded as the primary exposure variable in the dataset. Only cases in which the variant classification could be determined by the assay were retained for the final analysis.

Clinical and demographic data were collected using a structured questionnaire adapted from the World Health Organization Global COVID-19 Clinical Platform Case Report Form (CRF), which has been widely used for standardized symptom reporting in COVID-19 research and surveillance (30). Interviews were conducted by trained health professionals who received standardized training on questionnaire administration to minimize interviewer variability. The questionnaire captured demographic characteristics (age, sex, occupation, and geographic division), clinical symptoms experienced during the acute phase of infection, and the presence of pre-existing medical conditions. Symptom variables included fever, cough, sore throat, body aches, headache, shortness of breath, loss of smell, loss of taste, fatigue, nausea, vomiting, diarrhea, gastrointestinal disturbances, rhinorrhea, chills, and rigors. Participants were asked to report symptoms experienced during their confirmed COVID-19 illness episode. Data were recorded in a structured electronic dataset and cross-checked against laboratory identifiers to ensure accuracy.

The primary outcome variables were the clinical characteristics associated with SARS-CoV-2 infection, operationalized as the presence or absence of specific symptoms during the infection episode. Secondary outcome variables included the presence of pre-existing comorbid conditions such as hypertension, diabetes mellitus, asthma, chronic obstructive pulmonary disease, cardiovascular disease, chronic kidney disease, obesity, and other chronic illnesses. The primary exposure variable was SARS-CoV-2 variant classification (Alpha, Beta, Gamma, or Delta). Sociodemographic variables including age, gender, occupation, and geographic division were included as potential confounders. Age was treated as a continuous variable in descriptive analysis and categorized where appropriate for subgroup comparisons. Symptom variables were coded as binary outcomes based on participant self-report during interviews.

Several methodological steps were implemented to minimize potential sources of bias. To reduce interviewer bias, all data collectors used the same standardized questionnaire and received training before data collection. Recall bias was addressed by restricting symptom reporting to the acute infection episode documented in the laboratory database. Selection bias was minimized by contacting all eligible participants within the laboratory registry rather than sampling from a subset of records. Data integrity procedures included double verification of variant classification against laboratory records and consistency checks within the dataset prior to analysis. Variables with incomplete responses were reviewed and cross-checked during follow-up calls when possible to reduce missing information.

The sample size was determined based on the number of eligible PCR-confirmed cases available in the PHRL registry that met the inclusion criteria and could be successfully contacted for participation. The final analytical dataset consisted of 416 participants with confirmed variant classification and completed clinical interviews. This sample size provided adequate representation of the predominant circulating variants during the study period and allowed comparison of symptom distributions between variant groups.

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were calculated for demographic characteristics and clinical symptoms. Continuous variables were summarized using means and standard deviations, while categorical variables were presented as frequencies and percentages. The association between SARS-CoV-2 variant type and categorical variables such as symptoms, gender, occupation, and comorbidities was assessed using the Pearson chi-square test. When expected cell counts were small, Fisher's exact test or the Fisher–Freeman–Halton test was applied to ensure valid inference. Monte Carlo simulation with a two-sided 95% confidence interval was used to estimate exact p-values where appropriate. Statistical significance was defined as a two-tailed p-value of less than 0.05. Sensitivity analyses were conducted to verify the

robustness of the results by examining symptom distributions across variant groups after stratification by demographic variables.

All data were anonymized prior to analysis to protect participant confidentiality. The study protocol was reviewed and approved by the Ethics Review Board of Khyber Medical University (Approval ID: KMU/IPHSS/Ethics/2023/CP/089). The study adhered to the ethical principles outlined in the Declaration of Helsinki and followed international ethical standards for research involving human participants (31). Verbal informed consent was obtained from all participants before conducting the telephone interview. Data were stored in password-protected electronic files accessible only to the research team to ensure data security and integrity.

RESULTS

Among the 416 participants included in the analysis, the Delta variant constituted the overwhelming majority of infections, accounting for 310 cases (74.5%; 95% CI: 70.3%–78.7%). Gamma was the second most frequent variant with 60 cases (14.4%; 95% CI: 11.1%–17.8%), followed by Alpha with 36 cases (8.7%; 95% CI: 6.0%–11.4%) and Beta with 10 cases (2.4%; 95% CI: 1.0%–4.6%). This distribution indicates that nearly three out of every four infections in the study population were attributed to the Delta variant, whereas Beta represented only a very small fraction of cases.

With respect to sociodemographic characteristics, males comprised 252 of the 416 participants (60.6%), while females accounted for 164 (39.4%). The distribution of variant type differed significantly by gender ($p=0.009$). Among Delta cases, 201 of 310 participants were male (64.8%) and 109 (35.2%) were female, showing a clear male predominance. In contrast, Alpha cases were slightly more frequent in females, with 19 of 36 cases (52.8%) occurring in women and 17 (47.2%) in men. Gamma also showed a modest female predominance, with 32 of 60 cases (53.3%) among females and 28 (46.7%) among males. Beta remained numerically small, but 6 of 10 cases (60.0%) occurred in males. Employment status did not differ significantly across variants ($p=0.41$). Students represented the largest occupational group overall, with 118 participants in total, including 13 Alpha cases (36.1% of Alpha), 3 Beta cases (30.0% of Beta), 18 Gamma cases (30.0% of Gamma), and 84 Delta cases (27.1% of Delta). Private employees formed the second largest group, contributing 104 participants overall, including 10 Alpha cases (27.8%), 3 Beta cases (30.0%), 18 Gamma cases (30.0%), and 73 Delta cases (23.5%). Government employees were relatively more represented in Gamma and Delta infections, accounting for 14 of 60 Gamma cases (23.3%) and 65 of 310 Delta cases (21.0%).

The overall clinical profile of the study population was dominated by respiratory and constitutional symptoms. Cough was the most frequently reported symptom, present in 406 of 416 participants (97.6%; 95% CI: 95.9%–98.8%), followed by fever, body aches, and sore throat, each reported by 403 participants (96.9%; 95% CI: 95.0%–98.3%). Headache was reported by 300 participants (72.1%; 95% CI: 67.5%–76.2%), while loss of smell and loss of taste were also highly prevalent, affecting 316 (75.8%; 95% CI: 71.4%–79.6%) and 315 (75.7%; 95% CI: 71.3%–79.5%) participants, respectively. Gastrointestinal manifestations were not uncommon: nausea was present in 242 participants (58.2%; 95% CI: 53.3%–62.9%), gastrointestinal problems in 176 (42.3%; 95% CI: 37.6%–47.1%), and diarrhea in 153 (36.8%; 95% CI: 32.2%–41.6%). Less frequent features included rigors in 128 participants (30.7%), fatigue in 105 (25.2%), shortness of breath in 93 (22.4%), rhinorrhea in 60 (14.4%), chills in 60 (14.4%), vomiting in 23 (5.5%), and asymptomatic infection in 25 participants (6.0%).

Marked variation in symptom patterns was observed across the four variants, and most comparisons were statistically significant. Fever, sore throat, and body aches were present in 302 of 310 Delta cases (97.4%) compared with 56 of 60 Gamma cases (93.3%), 26 of 36 Alpha cases (72.2%), and 7 of 10 Beta cases (70.0%), with all three comparisons showing strong evidence of association with variant type ($p<0.001$). The odds of fever, sore throat, and body aches were each substantially higher in Delta compared with the other variants combined, with an odds ratio of 4.82. Headache demonstrated an even

more pronounced pattern, occurring in 286 Delta cases (92.2%) but only 12 Alpha cases (33.3%), 1 Beta case (10.0%), and 1 Gamma case (1.7%), corresponding to an odds ratio of 9.41 for Delta versus the other variants and a p-value of less than 0.001.

Sensory symptoms were strongly concentrated in Delta infections. Loss of smell was reported in 299 of 310 Delta cases (96.4%), compared with only 12 of 36 Alpha cases (33.3%), 2 of 10 Beta cases (20.0%), and 3 of 60 Gamma cases (5.0%), yielding an odds ratio of 8.96 and a highly significant association ($p<0.001$). A similar pattern was observed for loss of taste, which affected 294 Delta cases (94.8%) but only 13 Alpha cases (36.1%), no Beta cases, and 8 Gamma cases (13.3%), with an odds ratio of 8.51 and $p<0.001$. Cough was also common across all variants but remained most prevalent in Delta and Gamma, occurring in 302 Delta cases (97.4%) and 56 Gamma cases (93.3%), compared with 25 Alpha cases (69.4%) and 7 Beta cases (70.0%), with an odds ratio of 5.12 for Delta versus the other variants and $p<0.001$.

Gastrointestinal and systemic manifestations showed a different distribution. Nausea affected 219 of 310 Delta cases (70.6%) and 7 of 10 Beta cases (70.0%), but was less common in Alpha (13 of 36; 36.1%) and absent in Gamma, with an overall significant association ($p<0.001$). Vomiting was concentrated in Alpha and Beta infections, reported in 13 Alpha cases (36.1%) and 7 Beta cases (70.0%), but only 3 Delta cases (1.0%) and no Gamma cases, corresponding to an odds ratio of 0.08 for Delta compared with other variants and $p<0.001$. Gastrointestinal problems were most prominent in Gamma, where they were reported in 55 of 60 participants (91.7%), followed by Beta in 6 of 10 participants (60.0%), Delta in 107 of 310 participants (34.5%), and Alpha in 8 of 36 participants (22.2%), again with strong statistical evidence of variation ($p<0.001$). Diarrhea was present in 136 Delta cases (43.9%), compared with 12 Gamma cases (20.0%), 2 Beta cases (20.0%), and 3 Alpha cases (8.3%), corresponding to an odds ratio of 2.67 and $p<0.001$.

Several symptoms were particularly concentrated in Gamma infections. Fatigue was reported in 56 of 60 Gamma cases (93.3%) and 32 of 36 Alpha cases (88.9%), compared with 7 of 10 Beta cases (70.0%) and only 10 of 310 Delta cases (3.2%), with Delta showing markedly lower odds relative to the other variants (OR 0.02; $p<0.001$). Rigors were absent in Alpha and Beta but present in 56 Gamma cases (93.3%) and 58 Delta cases (18.7%), with a significant association ($p<0.001$). Chills showed a similar pattern, occurring in 56 Gamma cases (93.3%) but only 6 Delta cases (1.9%) and none of the Alpha or Beta cases, with an odds ratio of 0.02 for Delta versus other variants and $p<0.001$.

Shortness of breath was most frequent in Gamma and Beta, affecting 56 of 60 Gamma cases (93.3%) and 7 of 10 Beta cases (70.0%), compared with 14 of 36 Alpha cases (38.9%) and only 16 of 310 Delta cases (5.2%), with an odds ratio of 0.07 for Delta and $p<0.001$. Rhinorrhea was almost entirely confined to Gamma, where it affected 56 of 60 participants (93.3%), while only 4 Delta cases (1.3%) reported it and no Alpha or Beta cases did so, producing another highly significant result ($p<0.001$). Asymptomatic infection was most frequent in Beta and Alpha, occurring in 3 of 10 Beta cases (30.0%) and 10 of 36 Alpha cases (27.8%), compared with 4 of 60 Gamma cases (6.7%) and 8 of 310 Delta cases (2.6%), with an odds ratio of 0.19 for Delta and $p<0.001$.

Table 1 Distribution of SARS-CoV-2 variants among study participants (N = 416)

Variant	Frequency (n)	Percentage (%)	95% CI
Alpha	36	8.7	6.0–11.4
Beta	10	2.4	1.0–4.6
Gamma	60	14.4	11.1–17.8
Delta	310	74.5	70.3–78.7

Total	416	100

Table 2 Sociodemographic characteristics of participants by SARS-CoV-2 variant (N = 416)

Characteristic	Alpha n (%)	Beta n (%)	Gamma n (%)	Delta n (%)	p-value
Gender					0.009*
Male	17 (47.2)	6 (60.0)	28 (46.7)	201 (64.8)	
Female	19 (52.8)	4 (40.0)	32 (53.3)	109 (35.2)	
Employment Status					0.41
Student	13 (36.1)	3 (30.0)	18 (30.0)	84 (27.1)	
Private employee	10 (27.8)	3 (30.0)	18 (30.0)	73 (23.5)	
Government employee	4 (11.1)	1 (10.0)	14 (23.3)	65 (21.0)	
Housewife	7 (19.4)	2 (20.0)	8 (13.3)	38 (12.3)	
Self-employed	0	1 (10.0)	2 (3.3)	33 (10.6)	
Unemployed	0	0	0	10 (3.2)	
Retired	2 (5.6)	0	0	7 (2.3)	

Table 3 Overall prevalence of clinical symptoms among participants (N = 416)

Symptom	Frequency (n)	Percentage (%)	95% CI
Cough	406	97.6	95.9–98.8
Fever	403	96.9	95.0–98.3
Body aches	403	96.9	95.0–98.3
Sore throat	403	96.9	95.0–98.3
Headache	300	72.1	67.5–76.2
Loss of smell	316	75.8	71.4–79.6
Loss of taste	315	75.7	71.3–79.5
Nausea	242	58.2	53.3–62.9
Gastrointestinal problems	176	42.3	37.6–47.1
Diarrhoea	153	36.8	32.2–41.6
Rigors	128	30.7	26.4–35.4
Fatigue	105	25.2	21.1–29.7
Shortness of breath	93	22.4	18.5–26.6
Rhinorrhea	60	14.4	11.2–18.2
Chills	60	14.4	11.2–18.2

Symptom	Frequency (n)	Percentage (%)	95% CI
Vomiting	23	5.5	3.5–8.1
Asymptomatic	25	6.0	3.9–8.7

Table 4 Clinical characteristics of SARS-CoV-2 variants

Symptom	Alpha n (%)	Beta n (%)	Gamma n (%)	Delta n (%)	Odds Ratio (Delta vs Others)	p-value
Fever	26 (72.2)	7 (70.0)	56 (93.3)	302 (97.4)	4.82	<0.001
Sore throat	26 (72.2)	7 (70.0)	56 (93.3)	302 (97.4)	4.82	<0.001
Body aches	26 (72.2)	7 (70.0)	56 (93.3)	302 (97.4)	4.82	<0.001
Headache	12 (33.3)	1 (10.0)	1 (1.7)	286 (92.2)	9.41	<0.001
Loss of smell	12 (33.3)	2 (20.0)	3 (5.0)	299 (96.4)	8.96	<0.001
Loss of taste	13 (36.1)	0	8 (13.3)	294 (94.8)	8.51	<0.001
Nausea	13 (36.1)	7 (70.0)	0	219 (70.6)	2.74	<0.001
Vomiting	13 (36.1)	7 (70.0)	0	3 (1.0)	0.08	<0.001
GI problems	8 (22.2)	6 (60.0)	55 (91.7)	107 (34.5)	0.41	<0.001
Diarrhoea	3 (8.3)	2 (20.0)	12 (20.0)	136 (43.9)	2.67	<0.001
Cough	25 (69.4)	7 (70.0)	56 (93.3)	302 (97.4)	5.12	<0.001
Fatigue	32 (88.9)	7 (70.0)	56 (93.3)	10 (3.2)	0.02	<0.001
Rigors	0	0	56 (93.3)	58 (18.7)	0.18	<0.001
Chills	0	0	56 (93.3)	6 (1.9)	0.02	<0.001
Shortness of breath	14 (38.9)	7 (70.0)	56 (93.3)	16 (5.2)	0.07	<0.001
Rhinorrhea	0	0	56 (93.3)	4 (1.3)	0.03	<0.001
Asymptomatic	10 (27.8)	3 (30.0)	4 (6.7)	8 (2.6)	0.19	<0.001

Table 5 Distribution of comorbid conditions by SARS-CoV-2 variant

Comorbidity	Alpha	Beta	Gamma	Delta	Total	p-value
None	16	6	45	193	260	
Asthma	4	2	1	6	13	
Duodenal ulcer	2	0	3	22	27	
Obesity	3	1	2	21	27	
Hypertension	3	1	2	23	29	
COPD	0	0	2	3	5	
Diabetes mellitus	3	1	3	20	27	
Coronary heart disease	0	0	0	6	6	
Chronic kidney disease	2	0	0	2	4	
Dialysis	0	0	1	0	1	
Chronic liver disease	0	0	0	4	4	
Stroke	2	0	0	4	6	
Others	1	0	0	6	7	
Total	36	10	60	310	416	0.020

The distribution of comorbid conditions also varied significantly by variant group. Overall, 260 of 416 participants (62.5%) reported no comorbid condition, and among these, Delta remained the predominant variant, accounting for 193 cases, followed by Gamma with 45, Alpha with 16, and Beta with 6. Among participants with specific comorbidities, hypertension was reported in 29 individuals, of whom 23 had Delta, 3 had Alpha, 2 had Gamma, and 1 had Beta. Diabetes mellitus was present in 27 participants, including 20 Delta cases, 3 Alpha cases, 3 Gamma cases, and 1 Beta case.

Obesity was also observed in 27 participants, with 21 Delta cases, 3 Alpha cases, 2 Gamma cases, and 1 Beta case. Duodenal ulcer was recorded in 27 participants, of whom 22 had Delta and 3 had Gamma. Less common conditions were also predominantly represented among Delta infections, including all 6 coronary heart disease cases, all 4 chronic liver disease cases, 4 of 6 stroke cases, and 3 of 5 chronic obstructive pulmonary disease cases.

The overall association between variant type and comorbidity profile was statistically significant, with Pearson's chi-square equal to 62.534 (df=36, p=0.004), the likelihood ratio equal to 54.701 (df=36, p=0.024), and the Fisher–Freeman–Halton exact test yielding p=0.020. Collectively, these data indicate that although most participants had no underlying illness, the burden of reported comorbidity was numerically highest in Delta infections, consistent with the dominance of that variant in the study population.

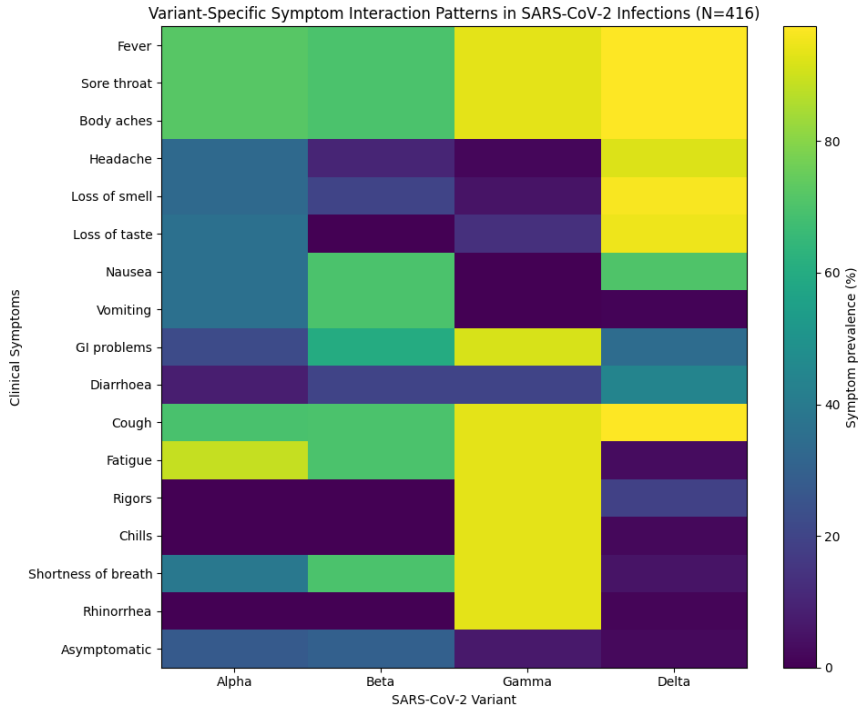

Figure 1 Variant-Specific Symptom Interaction Patterns In SARS-CoV-2 Infections (N=416)

The heatmap reveals distinct variant–symptom interaction patterns across the four SARS-CoV-2 variants. Respiratory and constitutional symptoms show the strongest clustering in Delta infections, where fever, sore throat, body aches, cough, loss of smell, and loss of taste exceed 94–97% prevalence, indicating a highly consistent respiratory phenotype. In contrast, Gamma infections demonstrate a different clinical cluster, with extremely high prevalence of systemic and upper-airway symptoms including fatigue (93.3%), rigors (93.3%), chills (93.3%), rhinorrhea (93.3%), and shortness of breath (93.3%), suggesting a broader systemic inflammatory profile. Beta infections show the strongest gastrointestinal signal, with nausea and vomiting each affecting 70% of cases, substantially higher than in other variants. Meanwhile, Alpha infections display a comparatively milder distribution, including the highest asymptomatic proportion (27.8%) and generally lower prevalence across most symptoms. The visualization therefore highlights three clinically meaningful gradients: Delta-dominant respiratory presentation, Gamma-dominant systemic response, and Beta-dominant gastrointestinal involvement, demonstrating clear heterogeneity in clinical phenotypes across variants.

DISCUSSION

This study evaluated the clinical characteristics associated with four major SARS-CoV-2 variants—Alpha, Beta, Gamma, and Delta—among PCR-confirmed cases in Khyber Pakhtunkhwa, Pakistan. The findings demonstrate clear heterogeneity in symptom profiles across variants, with Delta infections representing the overwhelming majority of cases and showing the highest prevalence of respiratory and constitutional symptoms. Specifically, fever, sore throat, body aches, and cough occurred in more than 97% of Delta infections, while sensory symptoms such as loss of smell and taste exceeded 94%. These findings are consistent with epidemiological investigations conducted during the global Delta surge, which documented higher transmissibility and increased symptomatic burden associated with the B.1.617.2 lineage compared with earlier variants (32). Similar clinical patterns have been described in studies from Europe and Asia, where Delta infections were characterized by a higher prevalence of systemic symptoms and more pronounced upper respiratory tract involvement (33).

The present analysis also identified a distinct symptom distribution for the Gamma variant, which demonstrated particularly high prevalence of systemic and inflammatory manifestations including fatigue, rigors, chills, rhinorrhea, and shortness of breath. Each of these symptoms affected more than

90% of Gamma-infected participants in the cohort. Previous studies have suggested that the Gamma variant may trigger stronger inflammatory responses compared with earlier strains, possibly due to spike protein mutations affecting viral entry and immune evasion mechanisms (34). Although the sample size for Gamma infections in this study was smaller than for Delta, the consistent clustering of systemic symptoms suggests the presence of a variant-specific clinical phenotype that warrants further investigation.

In contrast, Beta infections were characterized primarily by gastrointestinal symptoms, with nausea and vomiting each reported in approximately 70% of affected participants. This pattern differs from the predominantly respiratory manifestations observed in Delta infections and supports evidence from previous clinical investigations indicating that certain variants may influence tissue tropism and symptom presentation (35). The gastrointestinal involvement observed in Beta infections aligns with systematic reviews demonstrating that SARS-CoV-2 can infect gastrointestinal epithelial cells via ACE2 receptors, leading to symptoms such as nausea, vomiting, and diarrhea (36). While the Beta sample in the present study was limited, the prominence of gastrointestinal symptoms suggests that variant-specific host–virus interactions may influence the clinical spectrum of disease.

Another notable observation from this study was the comparatively milder clinical presentation associated with the Alpha variant. Alpha infections displayed lower overall symptom prevalence and the highest proportion of asymptomatic cases, reaching nearly 28% of participants. This finding is consistent with early pandemic reports indicating that a substantial proportion of Alpha infections were either asymptomatic or mildly symptomatic despite increased transmissibility (37). The presence of asymptomatic cases has important implications for transmission dynamics because individuals without symptoms may unknowingly contribute to viral spread in the community.

The distribution of comorbid conditions among infected participants showed that most individuals in the study population did not report underlying diseases. Among those with comorbidities, hypertension, diabetes mellitus, obesity, and duodenal ulcer were the most commonly reported conditions. Delta infections accounted for the majority of cases across nearly all comorbidity categories, which largely reflects the dominant prevalence of the Delta variant during the study period. Previous studies have shown that comorbidities such as hypertension and diabetes are associated with increased risk of severe COVID-19 outcomes, particularly among older individuals (38). However, the relatively young mean age of participants in this study may explain the lower overall prevalence of chronic diseases compared with cohorts from hospital-based studies.

The findings of this study have important public health implications, particularly in resource-limited settings where genomic sequencing capacity is constrained. Identifying variant-specific symptom clusters may assist clinicians and surveillance systems in recognizing circulating variants based on clinical presentation when molecular characterization is unavailable. Such information can support targeted diagnostic strategies, clinical triage, and outbreak response measures. Furthermore, understanding how symptom patterns vary between variants contributes to broader epidemiological surveillance and may improve early detection of emerging variants with altered pathogenicity.

Despite these contributions, several limitations should be acknowledged. First, the study relied on retrospective symptom reporting through telephone interviews, which introduces the possibility of recall bias. Second, the cross-sectional design prevents causal inference regarding relationships between variant type and clinical manifestations. Third, variant identification was based on mutation-specific PCR assays rather than full genomic sequencing, which may limit the precision of lineage classification. Fourth, the number of participants infected with Beta and Alpha variants was relatively small compared with Delta, which may affect the stability of estimates for these groups. Finally, the study population was drawn from a single provincial laboratory registry, which may limit the generalizability of the findings to other regions or populations.

Future studies incorporating prospective clinical follow-up, genomic sequencing, and larger multi-center cohorts will be important to further elucidate the relationship between SARS-CoV-2 genetic variation and clinical presentation. Such investigations will help refine our understanding of how viral evolution influences disease patterns and will contribute to improved preparedness for future respiratory viral outbreaks (39).

CONCLUSION

This study provides evidence that SARS-CoV-2 variants circulating in Khyber Pakhtunkhwa exhibit distinct clinical presentation patterns. The Delta variant was the most prevalent strain and was strongly associated with respiratory and sensory symptoms such as fever, cough, sore throat, and loss of smell and taste. Gamma infections were characterized by pronounced systemic manifestations including fatigue, rigors, chills, and rhinorrhea, while Beta infections showed a comparatively higher prevalence of gastrointestinal symptoms such as nausea and vomiting. In contrast, Alpha infections demonstrated a milder clinical profile with the highest proportion of asymptomatic cases. These findings highlight the heterogeneity of COVID-19 clinical phenotypes across variants and emphasize the importance of continuous surveillance to monitor evolving symptom patterns. Improved recognition of variant-specific symptom clusters may support clinical diagnosis, enhance epidemiological monitoring, and strengthen preparedness for future viral outbreaks, particularly in settings with limited genomic sequencing capacity..

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