**I Type of manuscript- Review Article**

**Title: Investigating the FLiRT Variants of COVID-19: Is it An Emerging Concern?**

**Running title: Investigating the FLiRT Variants of COVID-19**

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**Words**

**Abstract-180**

**Manuscript-1000**

**• Data Availability Statement -We declare if data is being shared, we shall provide the data.**

**• Conflict of Interest statement -' no conflict of interest declared'**

**. Funding -nil**

**Authorship statement**

All authors state that they contributed to this publication according to the guidelines of the journal and that no part of this manuscript was plagiarized.

**Ethical Statement by all Authors:**

1. This material is the authors’ original work, which has not been previously published elsewhere.

2. The paper is not currently being considered for publication elsewhere.

3. The paper reflects the authors’ research and analysis truthfully and completely.

4. The paper properly credits the meaningful contributions of co-authors and co-researchers.

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**Title-Investigating the FLiRT Variants of COVID-19: Is it An Emerging Concern?**

**Abstract:** The ongoing COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to multiple waves of infections globally. As the virus continues to evolve, new variants have emerged, some with concerning changes in transmissibility and virulence. Among these variants, the " FLiRT Variants" have recently garnered attention due to their potential to alter the dynamics of transmission and disease severity. According to the Infectious Disease Society of America, the nickname ‘FLiRT’ is based on the technical names for their mutations. The FLiRT variants, particularly KP.2, seem to exhibit heightened transmissibility in comparison to earlier Omicron sub-variants. Additionally, they demonstrate a capacity to evade immunity conferred by prior infection and vaccines, although the full extent of this evasion is still being investigated

In this article, we review the characteristics of the FLiRT Variant, including its genetic mutations, epidemiological features, potential impact on public health measures, and implications for vaccine efficacy. We also discuss strategies for surveillance, prevention, and mitigation efforts to control the spread of this variant and mitigate its impact on global health.

**Keywords:** COVID-19, FLiRT Variants, severe acute respiratory syndrome coronavirus 2, SARS-CoV-2

**Introduction:** As the COVID-19 pandemic evolves, the emergence of novel variants of SARS-CoV-2 has drawn attention due to their potential to influence disease transmission, severity, and vaccine efficacy.1. The emergence of new variants can also have a deleterious impact on long –COVID with additional associated morbidity and mortality.2 The Flirt Variant, distinguished by specific genetic mutations seemed to emerge from a fresh cluster of variants detected through wastewater surveillance.3 Dubbed FLiRT, these variants pose a potential risk for triggering a resurgence of COVID infections, following a recent decline after the December spike. 4,5 These variants, distant relatives of Omicron, emerged from JN.1, the variant responsible for the spike in cases last winter. They're known as the "FLiRT" variants, named after specific mutations; one featuring "F" and "L," while another involves "R" and "T." FLiRT variant exhibits some worrisome attributes, including alterations in the spike protein, which contribute to the ability of SARS-CoV-2, the virus responsible for COVID-19, to establish itself, proliferate within the body, and induce illness in individuals. 4

**Genetic Characteristics of Flirt Variants:** FLiRT variants of SARS-CoV-2 exhibit distinctive mutations, particularly within the spike protein, which facilitates viral entry into host cells. Notable mutations such as E484K, N501Y, and others may confer advantages such as enhanced infectivity, altered antigenicity, or resistance to neutralizing antibodies.6,7 Understanding the genetic composition of Flirt variants is crucial for elucidating their phenotypic properties and potential implications for disease dynamics. Among the FLiRT family, a specific variant has garnered significant attention: KP.2, which comprised approximately 25% of newly sequenced cases during the two weeks concluding on Apr. 27, as per the data provided by the U.S. Centers for Disease Control and Prevention (CDC).8 Conversely, other FLiRT variants, such as KP.1.1, have not experienced the same level of proliferation in the U.S. at present.8,9

**Epidemiological Behavior and Transmission Dynamics:** Preliminary epidemiological data suggest that FLiRT variants may exhibit altered transmissibility compared to earlier strains of SARS-CoV-2.10 Studies have indicated increased secondary attack rates and accelerated spread within populations where FLiRT variants have been identified. Factors contributing to enhanced transmission may include changes in viral fitness, host susceptibility, and social dynamics. Comprehensive epidemiological investigations are necessary to elucidate the transmission dynamics of Flirt variants and inform public health responses. A recent preprint study published on the bioRxiv server has examined the virological traits of the FLiRT variant KP.2. According to the study, this variant has shown "enhanced transmissibility and resistance to immunity.11

**Clinical Implications and Disease Severity:** The clinical implications of FLiRT variants in terms of disease severity, clinical outcomes, and therapeutic response are currently an area of active research.4 While some variants may exhibit altered virulence or disease presentation, current evidence suggests that the clinical spectrum of COVID-19 associated with Flirt variants is largely similar to that of earlier strains.4,12However, ongoing surveillance and clinical studies are essential to monitor for any shifts in disease severity or clinical characteristics associated with Flirt variants. However, Dr Eric Topol, executive vice president at Scripps Research, has noted recently that KP.2 and its kin will probably lead to an increase in cases, though he suggests, "I have a feeling it won't be a substantial surge." He speculates it might resemble more of a "wavelet." This speculation is grounded in observations that individuals recently infected by the JN.1 variant appear to possess some degree of immunity against reinfection. Additionally, the virus has not undergone sufficient mutation to significantly diverge from previous strains. Supporting this notion, a recent study by researchers in Japan, which was released online before undergoing peer review, also suggests that KP.2 exhibits lower infectivity compared to JN.1. 4,5.13,14

Two initial studies, one conducted in Japan and another by researchers in China, both published online before undergoing peer review, indicate that FLiRT variants may possess a greater ability to evade immune protection conferred by vaccines compared to JN.1.4,5,11,14This is concerning, particularly considering that a significant portion of adults in the U.S., approximately 30%, received their most recent booster shot last autumn, implying that their immunity may be starting to diminish.4,5

**Surveillance and Management Strategies**: To effectively address the FLiRT variant of COVID-19, comprehensive surveillance and management strategies are imperative.15  Enhanced genomic surveillance efforts should be prioritized to swiftly detect and monitor the spread of FLiRT variants.16 This entails ramping up sequencing capabilities and establishing robust data-sharing networks among local, national, and international health authorities. Early detection and reporting of FLiRT variant cases are critical for initiating targeted public health interventions and implementing containment measures promptly. Furthermore, public health messaging should emphasize the importance of vaccination, adherence to preventive measures, and regular testing to curb transmission .4,17

In parallel, continuous evaluation of vaccine efficacy against FLiRT variants is essential to inform booster campaign strategies and vaccine development efforts .17 Vaccination has proven to undoubtedly and markedly decrease the severity of COVID-19 and post-COVID symptoms known as LONG COVID-19. 2Therefore it is expected that vaccination shall help limit the severity of this variant too. However, it should be kept in mind that no vaccine has an absolute 100% efficacy, and numerous “breakthrough infections” can still occur. 18 Therefore adaptive response plans should be devised, incorporating flexible public health interventions and surge capacity planning for healthcare systems to effectively manage potential spikes in FLiRT variant cases .19,20Community engagement initiatives should be fostered to empower individuals to take proactive measures and facilitate community-led approaches to mitigate transmission risks. By implementing these multifaceted surveillance and management strategies, public health authorities can mitigate the impact of the FLiRT variant and safeguard public health.19Additionally, proactive measures such as targeted testing, contact tracing, and vaccination campaigns can help mitigate the spread of Flirt variants and prevent further transmission within communities.

**Conclusion:**

The emergence of Flirt variants underscores the dynamic nature of the COVID-19 pandemic and highlights the importance of ongoing surveillance and research efforts. By elucidating the genetic, epidemiological, and clinical characteristics of Flirt variants, scientists and public health authorities can develop informed strategies to mitigate their impact on disease transmission, clinical outcomes, and vaccine effectiveness. Collaborative international efforts are essential to address the evolving threat posed by Flirt variants and ultimately control the spread of COVID-19.

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