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Genomic evolution and epidemiological impact of SARS-CoV-2 omicron subvariants in Taiwan, 2023–2025

Li-Teh Liu [a,1], Chao-Ju Chen [b,c], Po-Chih Chen [c,d], Chun-Hong Chen [e,f], Ping-Chang Lin [g], Ching-Yi Tsai [g], Shu-Hui Lin [h], Chen-Hsuan Lin [b], Yi-Ching Lin [b,c], Jih-Jin Tsai [b,g,i,*,2]

[a] *Department of Medical Laboratory Science and Biotechnology, College of Medical Technology, Chung Hwa University of Medical Technology, Tainan City, Taiwan*
[b] *School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung City, Taiwan*
[c] *Department of Laboratory Medicine, Kaohsiung Medical University Hospital, Kaohsiung City, Taiwan*
[d] *Department of Medical Laboratory Science and Biotechnology, College of Health Sciences, Kaohsiung Medical University, Kaohsiung City, Taiwan*
[e] *National Mosquito-Borne Diseases Control Research Center, National Health Research Institutes, Zhunan, Miaoli County, Taiwan*
[f] *National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Zhunan, Miaoli County, Taiwan*
[g] *Tropical Medicine Center, Kaohsiung Medical University Hospital, Kaohsiung City, Taiwan*
[h] *Infection Control Center, Kaohsiung Medical University Hospital, Kaohsiung City, Taiwan*
[i] *Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung City, Taiwan*

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ABSTRACT

Background: The continued evolution of SARS-CoV-2 Omicron sublineages requires ongoing genomic and epidemiological surveillance. This study investigated the genomic epidemiology, national trends, and clinical aspects of SARS-CoV-2 in Taiwan from November 2023 to February 2025.

Methods: We analyzed the molecular and clinical characteristics of a local cohort (n = 22) from southern Taiwan. Case and mortality trends were evaluated using nationwide surveillance data, considering changes in case definitions. Broader genomic surveillance included 1782 Taiwanese sequences from GISAID to characterize the distribution and evolution of Omicron subvariants, considering the rollout timeline of XBB.1.5 and JN.1 vaccines.

Results: Genomic surveillance revealed a major epidemiological shift driven by variant succession: JN.1 and its descendants (e.g., KP.2, KP.3) replaced XBB-related subvariants, coinciding with infection waves in early and mid-2024. A more stringent national case definition for "severe complicated COVID-19" implemented in September 2024, substantially altered epidemiological metrics, reducing reported cases but increasing case fatality. In the local cohort, no significant associations were observed between sex, age, Ct value, comorbidity number, or vaccination status and hospitalization or severity, likely due to limited sample size. Nationally, individuals aged ≥ 65 years were disproportionately represented among severe cases and deaths, with risk amplified in those with comorbidities and low recent XBB.1.5/JN.1 vaccination coverage.

Conclusions: Taiwan experienced dynamic evolution of SARS-CoV-2 Omicron, dominated by JN.1 and its derivatives, which drove successive infection waves. Changes in national case definitions created substantial surveillance artifacts complicating interpretation of disease burden. Although national data reaffirm advanced age as the key risk factor for severe outcomes, these findings underscore the importance of targeted vaccination strategies and integrated surveillance systems capable of distinguishing the effects of viral evolution from policy-driven reporting changes.

Abbreviations: ACE2, Angiotensin-converting enzyme 2; CCI, Charlson comorbidity index; CFR, Case fatality rate; COVID-19, Coronavirus disease 2019; CPE, Cytopathic effects; Ct, Cycle threshold; GISAID, Global Initiative on Sharing All Influenza Data; N, Nucleocapsid gene; RdRP, RNA-dependent RNA polymerase; QRT-PCR, Quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SNP, Single-nucleotide polymorphism; TCDC, Taiwan Centers for Disease Control; VOC, Variant of concern; VOI, Variant of interest; VTM, Viral transport medium; WGS, Whole genome sequencing

[*] Correspondence to: Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Medical University Hospital, 100, Tzyou 1st Rd, Kaohsiung City 807377, Taiwan.

E-mail address: jijits@cc.kmu.edu.tw (J.-J. Tsai).

[1] orcid.org/0000–0002-7993–7263
[2] orcid.org/0000–0003-2226–8916

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Introduction

The emergence and global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have posed significant challenges to public health systems. Since its discovery, SARS-CoV-2 has evolved into multiple variants of concern (VOCs), characterized by differences in transmissibility, immune evasion, and, in some cases, disease severity [1, 2]. The Omicron variant (B.1.1.529), first reported in late 2021, exhibits a marked transmission advantage over previous VOCs, such as Delta, due to extensive spike protein mutations that confer enhanced transmissibility and significant immune escape from vaccine- or infection-induced immunity. The pandemic's progression has since been defined by the sequential emergence of Omicron subvariants, each with distinct mutational profiles and epidemiological characteristics [3].

Continuous genomic surveillance is essential for monitoring SARS-CoV-2 evolution, enabling the early detection of emerging subvariants and tracking their geographic distribution and prevalence [4, 5]. These efforts guide assessments of vaccine efficacy, treatment effectiveness, and the adaptation of public health measures. Regional surveillance provides critical insights into local transmission dynamics and the introduction or establishment of specific subvariants within populations [1–3]. Although Taiwan maintained effective pandemic control during the early phases [6–8], it experienced three distinct waves of Omicron between December 2021 and October 2023 [8–10], emphasizing the need for continuous monitoring of ongoing viral evolution. However, comprehensive data on the epidemiological and genomic characteristics of SARS-CoV-2 in Taiwan beyond October 2023 remain limited. Understanding the circulating Omicron subvariants, their temporal dynamics, and associated clinical features is therefore critical for refining public health strategies and clinical management and constitutes the central aim of this study.

This study investigated the genomic and clinical epidemiology of SARS-CoV-2 in Taiwan from November 2023 to February 2025 by: [1] characterizing the molecular and clinical features of a patient cohort in southern Taiwan; [2] describing national Coronavirus disease 2019 (COVID-19) trends, including the influence of evolving case definitions; and [3] delineating the distribution and phylogeny of Omicron subvariants in Taiwan using data from Global Initiative on Sharing All Influenza Data (GISAID)(https://gisaid.org/) [5]. By integrating local clinical data, national epidemiological trends, and genomic surveillance, this study provides a comprehensive overview of the SARS-CoV-2 landscape in Taiwan during a recent phase of the pandemic.

Materials and methods

Sample collection

Nasopharyngeal swab specimens were prospectively collected from patients with suspected COVID-19 at Kaohsiung Medical University Hospital (KMUH), Kaohsiung City, Taiwan between November 2023 and February 2025. The Informed consent was obtained from all participants or their legal guardians prior to enrollment. Swabs were preserved in viral transport medium (VTM) (Creative Life Science, Taiwan) for subsequent analysis.

Patient and public involvement

In this retrospective study, analyses were conducted solely on de-identified clinical and genomic data collected as part of routine surveillance and patient care. Therefore, patients and the public were not directly involved in the design, recruitment, conduct, or dissemination plans of this specific research study. Furthermore, as this was an observational surveillance study, no randomization was performed for patient selection or treatment allocation.

SARS-CoV-2 genome detection by real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR)

SARS-CoV-2 RNA was detected using the cobas SARS-CoV-2 and Influenza A/B assay on the cobas Liat Analyzer platform (Roche Molecular Systems, Inc., Pleasanton, CA, USA). This automated system targets SARS-CoV-2-specific RNA-dependent RNA polymerase (RdRP) and nucleocapsid (N) genes, as well as conserved regions of influenza A matrix and influenza B nonstructural protein genes. Results were interpreted automatically as 'Detected' or 'Not Detected' by the cobas Liat Analyzer (Roche Molecular Systems, Inc., Pleasanton, CA, USA) [9, 10].

SARS-CoV-2 isolation in cell culture

All procedures involving live SARS-CoV-2, including virus isolation and culture, were conducted in the Tropical Medicine Center with a certified Biosafety Level 3 laboratory is authorized by the Central Epidemic Command Center in Taiwan to diagnose suspected COVID-19 patients, following institutional and national biosafety guidelines [6, 11, 12]. Virus isolation was attempted using Vero E6 cells cultured in DMEM supplemented with 10 % FBS and antibiotics. VTM samples confirmed positive by qRT-PCR were inoculated onto Vero E6 monolayers following established protocols [6, 11, 12]. Cytopathic effects (CPE), defined as virus-induced morphological changes such as cell rounding, detachment, or syncytium formation reflecting viral replication and damage, were monitored daily by phase contrast microscopy. Samples that did not develop CPE within 3 days underwent blind passage every 2–3 days for up to 21 days to enhance viral recovery.

PCR amplification and sanger sequencing of the spike gene

RNA was reverse transcribed using the HiScript III 1st Strand cDNA Synthesis Kit (Vazyme Biotech, China). Approximately 10 ng of cDNA was amplified at 250 nM with the Phanta Flash PCR Master Mix (Vazyme Biotech, China) using specific primers (Supplementary Table 1). PCR cycling was performed on an Applied Biosystems 9700 Thermocycler (98°C for 30 s; 40 cycles of 98°C for 10 s, 60°C for 5 s, 72°C for 5 s; final extension at 72°C for 1 min). Amplicons were purified with VAHTS DNA Clean Beads (Vazyme Biotech, China) and assessed for integrity, size, and quantity via MultiNA MCE 202 microchip electrophoresis (Shimadzu, Japan). Purified products were subjected to bidirectional Sanger sequencing using BigDye Terminator v3.1 (Applied Biosystems, USA) on an ABI 3730 Genetic Analyzer (Applied Biosystems, USA). Sequence data were analyzed using Sequencing Analysis Software v5.2 (Applied Biosystems, USA).

Spike gene sequence analysis and lineage identification

Sequences were aligned to the Wuhan-Hu-1/2019 reference genome (GenBank MN908947) to identify mutations relative to the ancestral strain. To contextualize Omicron evolution, mutations associated with single-nucleotide polymorphisms (SNPs) characteristic of the BA.2 lineage were also examined. Pango lineages [13] were assigned using Nextclade v3.13.2 [14] and confirmed by cross-referencing mutation profiles with Outbreak.info data [15]. We acknowledge that targeted S-gene sequencing, unlike whole genome sequencing (WGS), cannot de novo identify novel recombinant lineages. Our assignments of recombinant lineages (e.g., XEC) were made by matching our S-gene mutation profile to the characteristic Spike profile of established, WGS-defined reference variants in the Pango database.

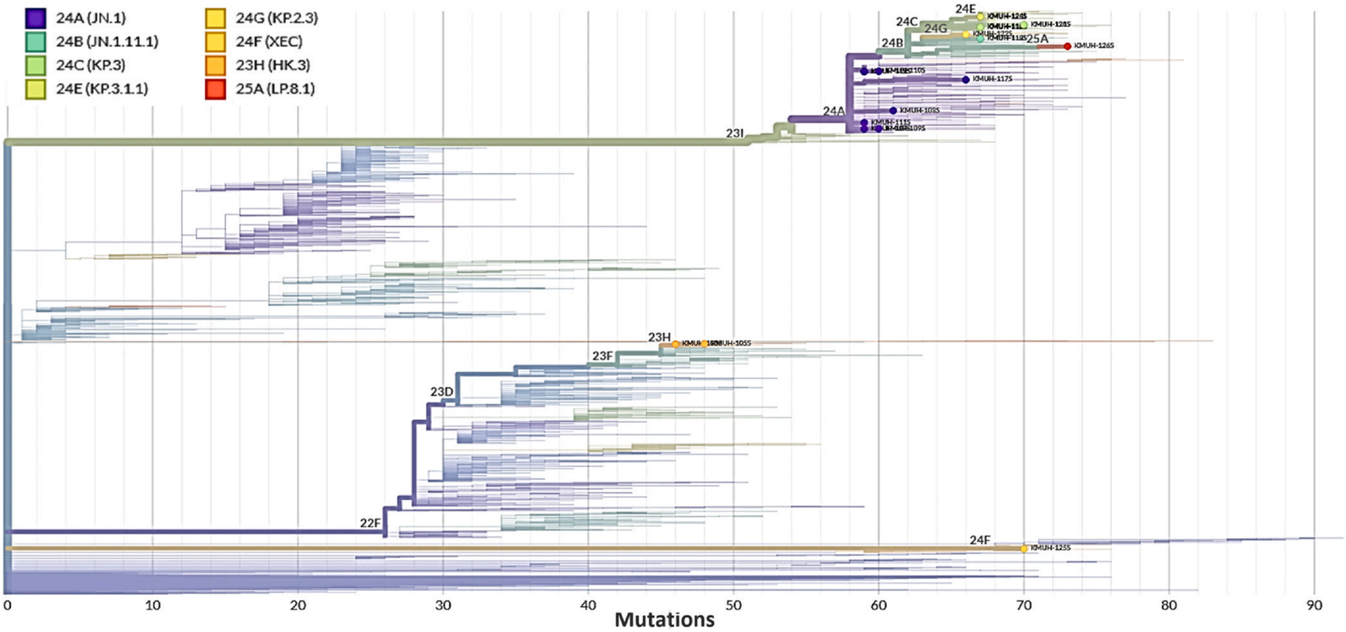

Fig. 1. Nextclade-based phylogenetic analysis of SARS-CoV-2 Omicron subvariants isolated in this study. Using Spike gene sequences, SARS-CoV-2 Omicron subvariants characterized in this study (labeled "KMUH" in the figure) were analyzed with Nextclade and mapped onto a global phylogenetic tree spanning Dec 2019 to Apr 2025. A partial tree depicting their placement results is presented. For detailed information on the clades and lineages of the SARS-CoV-2 Omicron subvariants isolated in this study, please refer to Table 1.

SARS-CoV-2 sequence data management and broader epidemiological context

Sequences generated in this study were deposited in GISAID EpiCoV [5] and GenBank. For comprehensive genomic epidemiology analysis of SARS-CoV-2 in Taiwan (November 2023 - February 2025), 1782 sequences meeting GISAID quality standards and collected in Taiwan during this period were compiled. Among these, 326 were associated with specific cities (160 Taipei City, 166 Tainan City), while the 22 isolates characterized in this study originated from Kaohsiung City (n = 20) and Pingtung County (n = 2). City information was unavailable for the remaining 1434 sequences. Phylogenetic analyses were performed using Nextclade v3.13.2 [14].

Retrieval of national and global COVID-19 epidemiological data

Taiwan's COVID-19 epidemiological data were obtained from the Taiwan National Communicable Disease Statistics System [16] and the National Notifiable Disease Surveillance Report [17], both maintained by the Taiwan Centers for Disease Control (TCDC). Global COVID-19 data were retrieved from Our World in Data (https://covid.ourworldindata.org/data/owid-covid-data.xlsx). These datasets are publicly accessible.

Statistical analysis

Descriptive statistics summarized patient demographics, clinical characteristics, epidemiological data, and viral indicators of the local cohort (n = 22). The Mann-Whitney *U* test compared continuous variables (e.g., age, Ct value—the PCR cycle threshold indicating viral load, comorbidity count) between two independent groups (e.g., hospitalized patients vs. non-hospitalized patients). The Kruskal-Wallis test analyzed continuous variables across three or more groups (e.g., COVID-19 severity levels). Due to small sample size, Fisher's exact test evaluated associations between categorical variables (e.g., sex, vaccination status, antiviral treatment) and outcomes such as hospitalization or disease severity. Spearman's rank correlation (rho) assessed relationships between monthly viral mutation indicators and epidemiological outcomes over 16 months (November 2023 - February 2025). Statistical significance was set at $P < 0.05$. Analyses were performed using MedCalc version 23.2.1 (MedCalc Software Ltd, Ostend, Belgium; 2025).

Results

Detection and molecular characterization of SARS-CoV-2 from clinical specimens

Of the 179 nasopharyngeal swabs collected, SARS-CoV-2 genomic RNA was detected in 47 samples by real-time qRT-PCR. Viral culture was attempted on these 47 RT-PCR positive samples, yielding CPE in 22 cultures. RT-PCR reconfirmed SARS-CoV-2 presence in these culture supernatants. These 22 isolates were prioritized for Spike gene sequencing. Phylogenetic analysis via Nextclade v3.13.2 (Fig. 1) classified all 22 isolates as Omicron subvariants, distributed as follows: 36.4 % (n = 8) 24 A, 9.1 % (n = 2) 24B, 22.7 % (n = 5) 24 C, 9.1 % (n = 2) 24E, 4.6 % (n = 1) 24 G, 4.6 % (n = 1) 24 F, 9.1 % (n = 2) 23 H, and 4.6 % (n = 1) 25 A (Table 1).

In this cohort of 22 SARS-CoV-2-infected patients, we analyzed the association between clinicopathological characteristics and disease outcomes (Table 1). Overall, no significant associations were observed for sex, age, Ct value, comorbidity count, and vaccination status with hospitalization or disease severity (all $P > 0.05$). Statistical analyses of antiviral efficacy and other factors were limited by small subgroup sizes, including only one death and five severe cases. The single fatality was a 61-year-old female with two comorbidities, severe COVID-19 (Ct 13), one vaccine dose, and Remdesivir treatment. Antiviral therapy was administered to 18 of 22 patients (81.8 %), including all severe (5/5) and moderate (5/5) cases, and most mild cases (8/12) [18, 19]. This treatment pattern reflects clinical guidelines prioritizing therapy for higher-risk or symptomatic individuals, introducing confounding by indication and precluding assessment of antiviral efficacy from these observational data. Overall, the principal statistically supported finding in this local cohort was the significant association between advanced age and hospitalization.

Table 1
Clinicopathological and Genomic Characteristics of SARS-CoV-2 Cases from the KMUH Cohort (November 2023 - February 2025).

seqName[a]	Clade	Pangolin lineage	Alias	Collection Date	Sex	Age[b]	Ct[c]	COVID-19	Vaccination Status[d]	Comorbidity[e]	Hospitalization[f]	Antiviral agents	Prognosis	GISAID[g]	GenBank
KMUH-105S	23 H	HK.3.3	XBB.1.9.2.5.1.1.3.3	2023–11–30	M	0	13	mild	None	0	4	-	Survival	19881011	PV687007
KMUH-106S	23 H	HK.3	XBB.1.9.2.5.1.1.3	2023–12–13	M	69	13	severe	M+M+M+M+M	4	12	+	Survival	19881022	PV687008
KMUH-107S	24 A	JN.1	BA.2.86.1.1	2024–01–15	M	66	11	severe	None	2	57	+	Survival	19881023	PV687009
KMUH-108S	24 A	JN.1.8.1	BA.2.86.1.1.8.1	2024–01–25	F	0	10	mild	None	0	-	-	Survival	19881024	PV687010
KMUH-109S	24 A	JN.1	BA.2.86.1.1	2024–04–09	M	0	11	mild	None	0	-	-	Survival	19881025	PV687011
KMUH-110S	24 A	JN.1.16	BA.2.86.1.1.16	2024–05–30	M	88	14	mild	M	3	-	+	Survival	19881027	PV687012
KMUH-111S	24 A	JN.1	BA.2.86.1.1	2024–06–04	M	72	13	moderate	M+M+M+M+M+M	2	3	+	Survival	19881028	PV687013
KMUH-112S	24 A	JN.1.16	BA.2.86.1.1.16	2024–06–11	F	90	12	mild	A+A+G+M	1	5	+	Survival	19881029	PV687014
KMUH-113S	24 A	JN.1.16	BA.2.86.1.1.16	2024–06–17	F	34	10	moderate	A+G+N	2	22	+	Survival	19881032	PV687015
KMUH-114S	24 C	KP.3.3	BA.2.86.1.1.11.1.3.3	2024–06–29	F	61	10	moderate	B+B+M	2	28	+	Survival	19881034	PV687016
KMUH-115S	24 C	KP.3.3	BA.2.86.1.1.11.1.3.3	2024–07–19	F	84	12	mild	A+A+M+M+M+M	3	-	+	Survival	19881035	PV687017
KMUH-116S	24 C	KP.3.3	BA.2.86.1.1.11.1.3.3	2024–07–25	M	35	11	mild	A+B+B+M	0	7	-	Survival	19881037	PV687018
KMUH-117S	24 A	LZ.2	BA.2.86.1.1.18.2.2	2024–08–04	F	77	16	severe	M+M+M	0	23	+	Survival	19881039	PV687019
KMUH-118S	24 B	KP.2.2	BA.2.86.1.1.11.1.2.2	2024–08–05	F	75	12	mild	M+M+M+M+M	1	12	+	Survival	19881041	PV687020
KMUH-119S	24 B	KP.2.2	BA.2.86.1.1.11.1.2.2	2024–08–14	M	81	11	moderate	M+M+M+M+M	1	7	+	Survival	19881042	PV687021
KMUH-120S	24 C	KP.3.3.1	BA.2.86.1.1.11.1.3.3.1	2024–08–30	F	61	13	severe	B	2	35	+	Death	19881058	PV687022
KMUH-121S	24 C	KP.3.3.1	BA.2.86.1.1.11.1.3.3.1	2024–09–02	F	37	17	mild	A+A+M+M	0	-	+	Survival	19881059	PV687023
KMUH-122S	24 G	KP.2.3	BA.2.86.1.1.11.1.2.3	2024–09–15	F	32	11	mild	A+A+B	2	110	+	Survival	19881060	PV687024
KMUH-123S	24 E	KP.3.1.1	BA.2.86.1.1.11.1.3.1.1	2024–09–25	M	78	14	severe	M+M+M+M	3	18	+	Survival	19881061	PV687025
KMUH-124S	24 E	KP.3.1.1	BA.2.86.1.1.11.1.3.1.1	2024–10–19	M	83	13	mild	G+G	6	27	+	Survival	19881062	PV687026
KMUH-125S	24 F	XEC	XEC	2025–01–08	F	64	12	mild	A+A+M+M	2	-	+	Survival	19881063	PV687027
KMUH-126S	25 A	LP.8.1.1	BA.2.86.1.1.11.1.1.1.3.8.1.1	2025–02–23	F	35	16	moderate	Bio+Bio+Bio	0	6	+	Survival	19881067	PV687028

[a] The sequence names associated with the SARS-CoV-2 Omicron variants uncovered in this study start with KMUH. A name with an "S" indicates that is a Spike gene sequence.

[b] Age is recorded in completed years. Patients KMUH-105S, KMUH-108S, and KMUH-109S were 11, 4, and 6 months old, respectively, at the time of diagnosis.

[c] Cycle threshold (Ct) values for SARS-CoV-2 genome real-time qRT-PCR.

[d] A: AstraZeneca; B: BNT; G: Medigen (MVC COVID-19 vaccine, made in Taiwan); M: Moderna; N: Novavax.

[e] Charlson comorbidity index (CCI) score.

[f] Length of stay (days). -: Outpatient Clinics (OPD).

[g] EPI_ISL_number.

Omicron-related COVID-19 in Taiwan (November 2023 - February 2025) epidemiological trends and surveillance indicators

Analysis of SARS-CoV-2 surveillance data in Taiwan from November 2023 to February 2025 (Table 2) indicates that local transmission was the primary driver of moderate/severe case burden from November 2023 to August 2024. Local cases peaked in January 2024, with a secondary surge in June - July 2024. Imported cases remained low. Mortality peaked in July 2024 with 436 reported deaths. During this period, the case fatality rate (CFR) ranged from 9.9 % (May 2024) to 12.8 % (July 2024), based on the March 20, 2023, definition that excluded mild cases and included only those classified as moderate/severe (i.e., requiring hospitalization or resulting in death).

From September 2024 onward, a revised and stricter case definition – limited to "severe complicated COVID-19" – led to a marked decline in reported cases: from 1194 in August 2024–176 in September 2024, and further down to 38 by February 2025. This shift contributed to an apparent increase in CFR, rising from 11.6 % (August 2024) to 21.0 % (September 2024), and peaking at 28.2 % in January 2025. However, this apparent increase is a statistical artifact. A direct comparison using the new, stricter definition across both months shows the opposite trend: the CFR for "severe complicated" cases in August was 27.3 % (6 deaths / 22 cases), which was higher than the 21.0 % (37 deaths / 176 cases) observed in September.

Age and sex distribution of COVID-19 cases across two surveillance periods (November 2023 - February 2025)

Age- and sex-stratified analysis (Table 3) revealed demographic trends across two surveillance periods defined by changes in case definitions. From November 2023 to August 2024, under the moderate/severe case reporting system, older age groups exhibited a higher burden of cases and deaths. Individuals aged ≥ 70 years accounted for the largest share, followed by those aged 60–69, who also demonstrated a significant impact. Notably, within the 30–39 age group, males had a significantly higher CFR than females ($P = 0.03$). Severe outcomes were infrequent among younger individuals. In the subsequent period (September 2024 - February 2025), defined by the more stringent criteria, cases and deaths remained highly concentrated in the elderly population (≥ 70 years), reflecting increased vulnerability to severe disease.

Table 2
Monthly COVID-19 data between November 2023 and February 2025. [a].

Year	Month	Imported	Autochthonous	Total	Death	CFR[b]
2023	November	8	1019	1027	119	11.6 %
	December	8	1324	1332	169	12.7 %
2024	January	12	2446	2458	297	12.1 %
	February	8	2376	2384	293	12.3 %
	March	7	1553	1560	163	10.4 %
	April	7	829	836	87	10.4 %
	May	5	1081	1086	108	9.9 %
	June	7	2853	2860	300	10.5 %
	July	9	3406	3415	436	12.8 %
	August[c]	6	1188	1194	139	11.6 %
	September	2	174	176	37	21.0 %
	October	1	114	115	26	22.6 %
	November	0	69	69	18	26.1 %
	December	1	51	52	9	16.7 %
2025	January	0	39	39	11	28.2 %
	February	0	38	38	6	15.8 %

[a] Data were retrieved from Taiwan National Infectious Disease Statistics System [16]. Taiwan Centers for Disease Control. Taiwan National Infectious Disease Statistics System. Available from: https://nidss.cdc.gov.tw/en/Home/Index. Accessed on April 26, 2025. Date Type: Date of Onset. People who tested positive for SARS-CoV-2 before March 19, 2023, were notifiable. On March 20, 2023, the case definition of Severe Pneumonia with Novel Pathogens was revised. Effective March 20, 2023, mild COVID-19 cases were exempt from reporting and isolation, and only patients who met the criteria for moderate or severe COVID-19 were notifiable. Case definition: People who tested positive for SARS-CoV-2 (via RT-PCR, virus culture, or spike protein antigen), developed a fever (≥ 38°C) or respiratory symptoms and, within 14 days (inclusive), develop pneumonia requiring oxygen therapy or other complications, resulting in hospitalization (including emergency department bed wait) or death. On September 1, 2024, "Severe Pneumonia with Novel Pathogens" was revised to "Severe Complicated COVID-19", along with an updated case definition. Case definition: People who tested positive for SARS-CoV-2 (via RT-PCR, virus culture, or spike protein antigen), developed a fever (≥ 38°C) or respiratory symptoms and develop pneumonia or other complications within 14 days (inclusive), requiring intensive care unit treatment or resulting in death.

[b] CFR: Case fatality rate.

[c] In August, there were 22 COVID-19 cases and 6 COVID-19-related deaths, applicable to the case definition effective from September 1, 2024.

Monitoring the circulation of SARS-CoV-2 in Taiwan (November 2023 - February 2025)

The temporal dynamics of COVID-19 cases and deaths are shown in Fig. 2. Monthly case counts showed a wave-like pattern, with mortality trends generally mirroring case trends (Fig. 2**A**). Age-specific analysis demonstrated higher case counts among individuals aged ≥ 65 years compared to those under 65, particularly during peak months (Fig. 2**B**). The older age group also experienced significantly more deaths each month (Fig. 2**C**). Across both age groups, death counts followed the trajectory of case incidence, typically with a time lag.

Genomic epidemiology and evolutionary dynamics of SARS-CoV-2 omicron subvariants in Taiwan

To investigate the clade and subvariant distribution of SARS-CoV-2 in Taiwan from November 2023 to February 2025, 1782 GISAID sequences were analyzed. As shown in Fig. 3**A**, JN.1 and its descendants – classified as variants of interest (VOI) – predominated, representing the majority of circulating strains. Other contributing lineages included EG.5-related variants, BA.2.86 derivatives excluding JN.1, and a smaller fraction of pre-VOC Omicron lineages (B.1.1.529 + BA.*). These findings indicate a dynamic, converging viral landscape dominated by JN.1-related variants.

Fig. 3**B** situates these 1782 Taiwanese sequences within the global phylogenetic context. They span multiple Nextclade designations and Pango lineages, reflecting the diversity of Omicron subvariants. A substantial proportion clustered in clade 24 A (JN.1) and its derivatives (e.g., 24B/KP.2, 24 C/KP.3), confirming JN.1 and its branches as dominant. Additional sequences were associated with early Omicron branches (e.g., 23H/HK.3, 23I/BA.2.86, 22 F/XBB, 23D/XBB.1.9) and more recent emergent branches (e.g., 24D/XDV.1, 24E/KP.3.1.1, 24 F/XEC, 24 G/KP.2.3), suggesting the co-circulation of diverse Omicron subvariants.

The temporal distribution of Pango lineages over the study period (November 2023 - February 2025) is shown in Fig. 3**C**. EG.5.1 and HK.3 were prominent in late 2023 (November - December), followed by a rapid shift beginning in early 2024, with JN.1 and its descendants (JN.1.*) becoming dominant by January through April - May. JN.1 remained prevalent, while newer subvariants such as JN.1.16, KP.1, KP.2, and KP.3 emerged, with KP.2 and KP.3 expanding throughout the second half of 2024. SXDV.1 and LB.1 emerged sporadically, and XEC appeared in early 2025. These trends reflect a rapid and sustained turnover of dominant lineages.

Monthly Nextclade subvariant distributions are further detailed in Fig. 3**D**. XBB-derived subvariants predominated in November-December 2023. Beginning in January 2024, BA.2.86.-related lineages, including JN.1, rapidly replaced XBB subvariants, maintaining dominance throughout most of 2024. BA.5.-related and earlier subvariants were infrequently detected. These patterns corroborate the major shift toward BA.2.86-derived viruses illustrated in Fig. 3**C**.

Table 3
Distribution of age and sex among confirmed COVID-19 patients and COVID-19-related mortality in Taiwan (November 2023 - February 2025).[a].

		November 2023–August 2024[b]				September 2024–February 2025[d]	
Age	Sex	COVID-19 cases	Deaths	CFR (%)	*P*-value[c]	COVID-19 cases	Deaths[e]
0–9	Female	65	2	3.1 %	0.49	2	111
	Male	75	1	1.3 %		3	
10–19	Female	20	0	0.0 %	0.42	1	
	Male	30	1	3.3 %		2	
20–29	Female	39	0	0.0 %	0.26	1	
	Male	60	2	3.3 %		2	
30–39	Female	99	1	1.0 %	0.03	1	
	Male	126	9	7.1 %		4	
40–49	Female	170	4	2.4 %	0.45	7	
	Male	329	12	3.6 %		9	
50–59	Female	407	18	4.4 %	0.85	13	
	Male	815	34	4.2 %		29	
60–69	Female	934	85	9.1 %	0.92	23	
	Male	2062	185	9.0 %		66	
70 +	Female	5411	720	13.3 %	0.51	132	
	Male	7487	1031	13.8 %		214	

[a] Data were retrieved from Taiwan National Infectious Disease Statistics System [16]. Taiwan Centers for Disease Control. Taiwan National Infectious Disease Statistics System. Available from: https://nidss.cdc.gov.tw/en/Home/Index. Accessed on April 26, 2025.

[b] Date Type: Date of Onset. One patient aged over 70 have unrecorded sex information. People who tested positive for SARS-CoV-2 before March 19, 2023, were notifiable. On March 20, 2023, the case definition of Severe Pneumonia with Novel Pathogens was revised. Effective March 20, 2023, mild COVID-19 cases were exempt from reporting and isolation, and only patients who met the criteria for moderate or severe COVID-19 were notifiable. Case definition: People who tested positive for SARS-CoV-2 (via RT-PCR, virus culture, or spike protein antigen), developed a fever (≥ 38°C) or respiratory symptoms and, within 14 days (inclusive), develop pneumonia requiring oxygen therapy or other complications, resulting in hospitalization (including emergency department bed wait) or death.

[c] Two-way Chi-squared test.

[d] Date Type: Date of Notification. On September 1, 2024, "Severe Pneumonia with Novel Pathogens" was revised to "Severe Complicated COVID-19", along with an updated case definition. Case definition: People who tested positive for SARS-CoV-2 (via RT-PCR, virus culture, or spike protein antigen), developed a fever (≥ 38°C) or respiratory symptoms and develop pneumonia or other complications within 14 days (inclusive), requiring intensive care unit treatment or resulting in death.

[e] During this period, the age group classifications differed from those used between November 2023 and August 2024. There were 13 deaths aged 19–64 years and 98 cases aged over 65 years; data on sex were unavailable. The numbers of fatal cases presented in Table 3 are identical to those in Fig. 2C but differ from those in Table 1, as they were obtained from separate datasets archived on the Taiwan CDC website.

Exploratory correlation of genomic and epidemiological trends

An exploratory Spearman rank correlation analysis investigated associations between average monthly SARS-CoV-2 viral mutations (nucleotide/amino acid substitutions, deletions, insertions) and COVID-19 epidemiological outcomes (age-stratified cases, deaths, CFR) in Taiwan (November 2023 - February 2025, n = 16 months). No widespread, significant correlations emerged. A more complex, regression-based approach to adjust for confounders was deemed inappropriate for two primary reasons: [1] the limited sample size (n = 16 months) lacks the statistical power for a valid multivariate model, and [2] the dataset is confounded by the September 2024 case definition change, which creates a major structural break in the time-series data. For example, average nucleotide substitutions did not significantly correlate with cases in individuals ≥ 65 years (rho = −0.10, p = 0.710), nor did average amino acid deletions significantly correlate with CFR in this group (rho = 0.27, p = 0.312). These limitations preclude definitive conclusions on direct causal relationships between these specific viral mutation patterns and observed epidemiological trends.

Discussion

Molecular analysis of 22 SARS-CoV-2 isolates from southern Taiwan revealed the co-circulation of multiple Omicron subvariants, reflecting global evolutionary trends and the emergence of BA.2.86 derivatives such as JN.1 and its clades KP.2 and KP.3 in 2024 [20–22]. This was corroborated by the analysis of 1782 Taiwanese GISAID sequences, which demonstrated predominance of JN.1 and its descendants (clade 24 A and related sublineages 24B, 24 C), displacing earlier XBB subvariants prevalent in late 2023. According to World Health Organization reports and genomic database [5, 23, 24], JN.1 rapidly became the dominant lineage worldwide by early 2024, displacing prior XBB subvariants. The subsequent global rise of KP.2 and KP.3 in mid-2024, characterized by spike protein mutations such as R346T, F456L, and V1104L, has been linked to enhanced immune evasion [3, 20, 21, 25, 26], a pattern mirrored in Taiwan's GISAID data. The primary epidemiological impact of this genomic evolution was the direct driving of new national infection waves. As shown in Fig. 2A and Fig. 3B&C, the replacement of XBB subvariants by JN.1 in early 2024 coincided with the first major case surge in January 2024. Subsequently, the emergence and expansion of 'FLiRT' variants, such as KP.2 and KP.3, coincided with the second and largest surge in June-July 2024. This linkage demonstrateed that the 'impact' was the variants' immune-evasive ability to fuel transmission, rather than an increase in intrinsic virulence. The continued emergence and co-circulation of these subvariants highlight the dynamic nature of SARS-CoV-2 evolution and the imperative for sustained genomic surveillance to monitor variant shifts, guide public health strategies, and drive future vaccine and therapeutic development.

This study presents a comprehensive overview of the SARS-CoV-2 landscape in Taiwan from November 2023 to February 2025, integrating local clinical data, national epidemiological trends, and genomic surveillance. This study also integrated a small, single-center descriptive cohort (n = 22) from southern Taiwan, no significant associations were found between sex, age, Ct value, number of comorbidities, or vaccination status and either hospitalization or disease severity, likely reflects the limited statistical power of the small sample size. National data suggest recent vaccination confers protection against severe COVID-19 in high-risk populations, this association was not statistically significant in the local cohort. The importance of age as a risk factor was highlighted by national epidemiological data indicating that individuals aged ≥ 65 years, particularly those with comorbidities and lower uptake of recent XBB.1.5/JN.1 vaccines, were disproportionately affected by severe outcomes and mortality. Furthermore, the introduction of a stricter case definition for "severe complicated COVID-19" in September 2024 resulted in a decline in reported cases but a concomitant increase in CFR, emphasizing the need for careful interpretation of surveillance data within evolving clinical criteria.

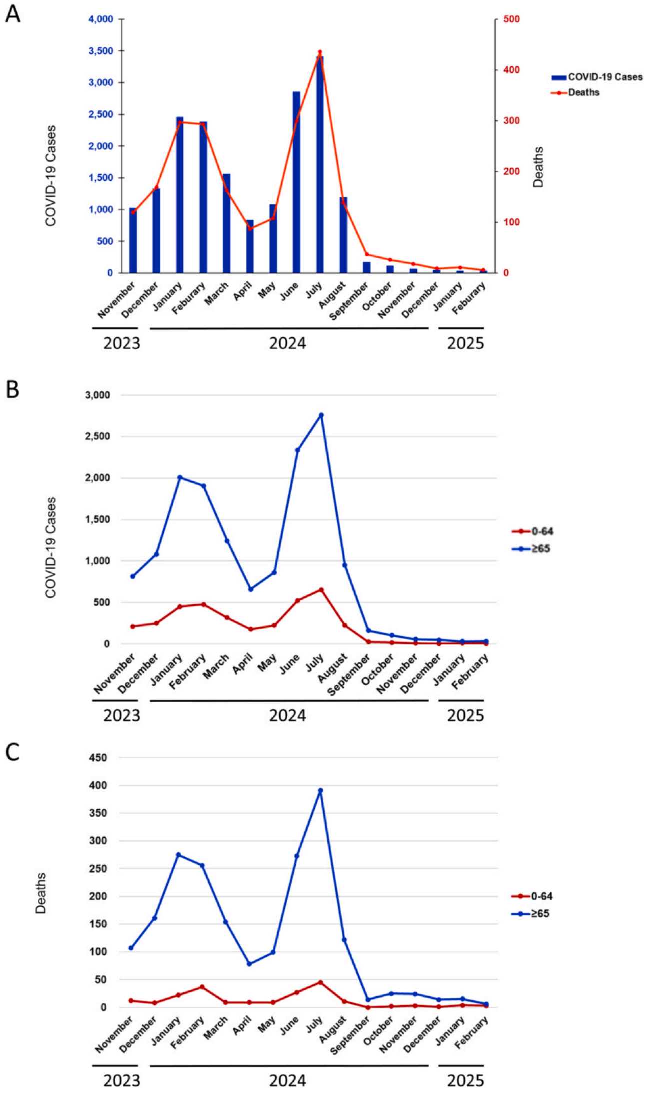

Fig. 2. Distribution of COVID-19 cases and deaths by age group: November 2023 to February 2025.(A) Distribution of COVID-19 cases and deaths. (B) Distribution of COVID-19 cases by age group (0–64 and ≥ 65 years). (C) Distribution of COVID-19-related deaths by age group (0–64 and ≥ 65 years).

Further analysis of global GISAID data (based on uploaded sequence counts from January 2024 to April 2025) revealed shifts in the global prevalence of JN.1-derived lineages, notably XEC and LP.8.1. Globally, XEC exhibited a significant increase toward late 2024, accounting for approximately 16.3 % of sequences in October 2024 and peaking at 34–36 % in December 2024 - January 2025. Meanwhile, the LP.8.1 lineage, and especially its subvariant LP.8.1.1, began to rise rapidly globally in late 2024, growing from a very rare presence (1 % of sequences) in December 2024–18.2 % in February 2025 and up to 37.0 % in March 2025, indicating its rapid surging prominence (https://gisaid.org/) [5]. In Taiwan, local emergence of these lineages (e.g., XEC and LP.8.1) was observed in the latter half of the study period (August 2024 - February 2025) (Fig. 3**C**), mirroring global trends. XEC, a recombinant variant, is associated with increased transmissibility, with some studies estimating its infectivity and immune evasion to surpass that of KP.3 [22]. In addition, XEC harbors mutations such as Q493E, linked to enhanced Angiotensin-converting enzyme 2 (ACE2) receptor binding affinity, which may facilitate both infectivity and immune escape [27, 28]. The rapid succession of these subvariants reflects ongoing global evolutionary dynamics, highlighting challenges for vaccine efficacy and treatment strategies, and necessitating flexible public health responses alongside sustained investment in broad or rapid countermeasures.

The JN.1 descendant LP.8.1 demonstrated high growth rates and XEC-like immune evasion due to spike mutations (e.g., Arg190Ser), while uniquely maintaining strong ACE2 binding affinity [29]. Although JN.1/KP.2-based vaccines induce neutralizing antibodies against LP.8.1 and XEC, their efficacy is reduced compared to original strains, suggesting partial immune escape [30]. The rollout of the XBB.1.5 vaccine (from September 26, 2023) likely exerted selection pressure against XBB-related subvariants in Taiwan by late 2023, coinciding with many countries' adoption of XBB-targeted vaccines as per global health recommendations. These monovalent vaccines were designed to enhance protection against circulating Omicron subvariants. The introduction of JN.1-targeted vaccines (from October 1, 2024) occurred after the establishment of JN.1 progeny (KP.2, KP.3) [17], following global recognition of JN.1 prevalence and subsequent vaccine formulation updates [31].

National epidemiological data show distinct phases influenced by changes in viral activity and reporting criteria. Significant local transmission waves occurred between November 2023 and August 2024, under moderate/severe case definitions (notably in January and June - July 2024). The adoption of a more stringent "severe complicated COVID-19" definition from September 1, 2024 resulted in fewer reported cases but a concurrently increased CFR, illustrating how administrative case definitions can confound surveillance interpretation, a key consideration in evolving public health strategies [32, 33]. This finding serves as a important cautionary note for epidemiological analysis: the artificial surge in CFR post-September 2024 should not be misinterpreted as an increase in viral virulence (e.g., from emerging KP variants). Our quantitative analysis suggests this was a statistical artifact. A direct comparison using the new, stricter definition across both months reveals that the CFR for 'severe complicated' cases in August was 27.3 % (6 deaths / 22 cases, please refer to Table 2 footnote c), which was higher than the 21.0 % (37 deaths / 176 cases) observed in September. This quantification confirms that the apparent CFR surge was an artifact of the changing denominator (i.e., the exclusion of 'moderate' cases), rather than a true increase in disease severity. This highlights the necessity to contextualize epidemiological data with prevailing definitions when comparing temporal or geographical disease burdens or assessing intervention effects. Taiwan's refinement of case definitions aligned with global trends during this phase of pandemic maturation, where many jurisdictions shifted to surveillance prioritizing severe illness and integrating COVID-19 into routine respiratory disease monitoring as population immunity increased [34]. Elevated CFRs in the later phase may primarily reflect a shift toward reporting only the most severe outcomes rather than focusing on intrinsic increases in viral virulence. Previous studies in Taiwan have also documented the impact of evolving case definitions and public health policies on COVID-19 indicators early in the pandemic [9, 10]. Correlation analysis between monthly viral mutations (GISAID data) and epidemiological outcomes (Taiwan CDC data) identified no statistically significant widespread associations, limited by small sample size (n = 16 months) and confounding changes in case definitions.

The statistically significant association between advanced age and hospitalization aligns with extensive global evidence confirming age as a major risk factor for severe COVID-19, including during the Omicron period [35–37]**.** A 2021 Taiwanese national cohort also reported increased risk of severe outcomes in older patients [38]. National data highlight the disproportionate burden borne by older adults, who accounted for approximately 80.7 % of cases and 90.9 % of deaths (moderate/severe definition) from November 2023 to August 2024, despite representing only 18.3–18.9 % of the population. Between March 2023 and September 2024 (old definition), 90.2 % (5031/5577) of deaths occurred in individuals aged ≥ 65 years, with 86.1 % (4801/5577) having chronic conditions. Notably, despite

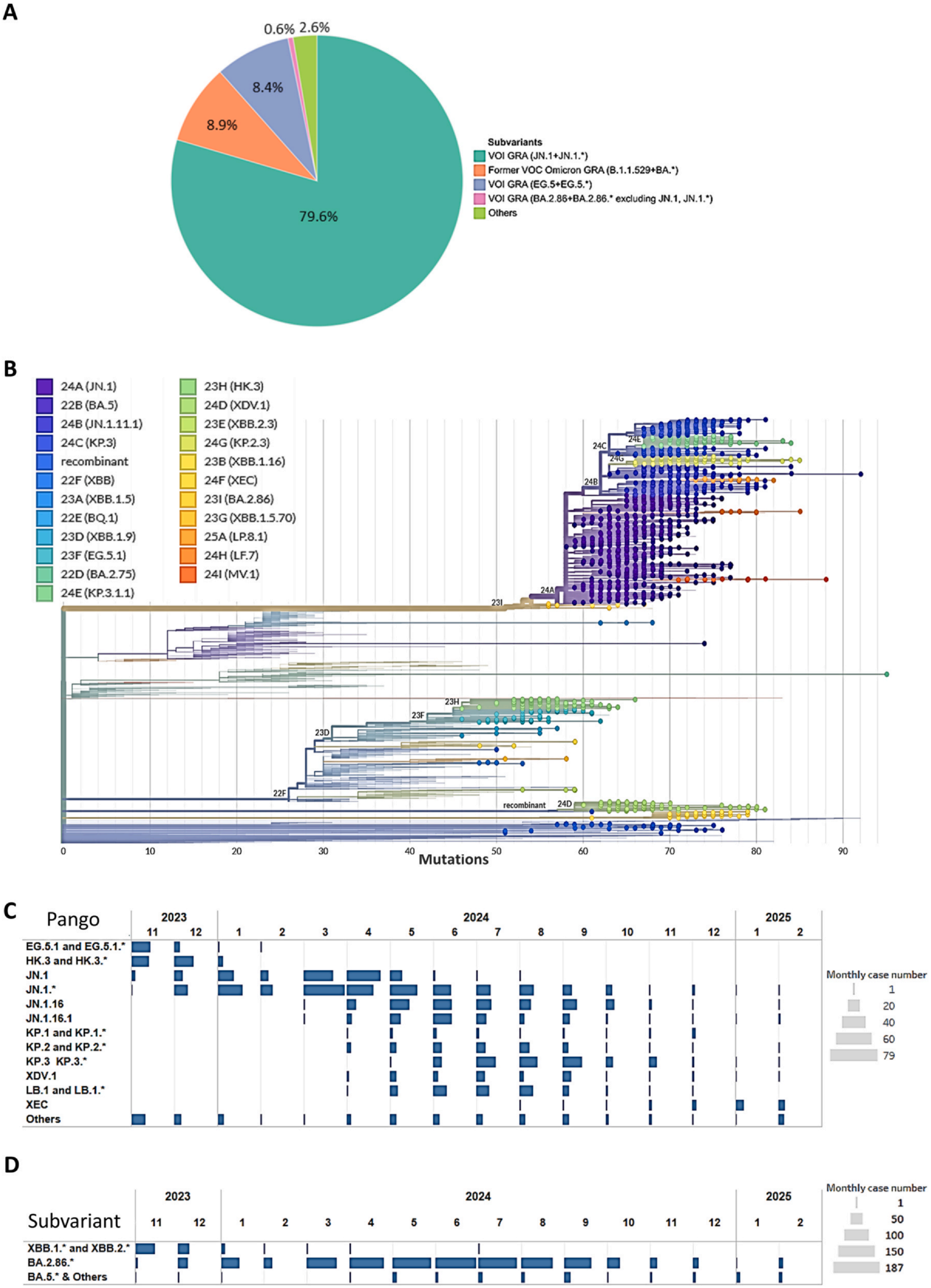

Fig. 3. Genomic surveillance of SARS-CoV-2 Omicron subvariants in Taiwan (November 2023 - February 2025, n = 1782).(A) Pie chart showing the proportional distribution of Omicron subvariants with a population frequency > 0.5 %; designations for Variant of Interest (VOI) and Variant of Concern (VOC) are noted. (B) Partial phylogenetic tree showing the placement of the 1782 Taiwanese SARS-CoV-2 sequences within a global SARS-CoV-2 phylogeny, differentiated by color-code (refer to figure for color key). (C) Monthly prevalence trends of major Pango lineages. (D) Monthly distribution of Omicron subvariants based on Nextclade classification.

availability of the XBB.1.5 vaccine from September 26, 2023, a large proportion (92.5 %) of deaths during this period occurred in unvaccinated individuals [17]. This disproportionate impact persisted under the stricter definition from September 2024 to February 2025: the ≥ 65 age group, constituting ~18.9–19.3 % of the population, accounted for ~77.8 % of severe complicated cases. For example, in weeks 36–39 of 2024 (new definition), 80.7 % (146/181) of local cases and all 14 deaths occurred in individuals ≥ 65 years, with 13 deaths among unvaccinated XBB individuals [16]. This disproportionately high mortality among the unvaccinated elderly highlights a gap in public health protection. It suggests the severe outcomes observed nationally were driven not only by viral evolution (e.g., JN.1/KP.2), but by the interaction of these immune-evasive variants with a specific, highly vulnerable, and under-vaccinated population, reinforcing the urgent importance of targeted vaccination campaigns [10]. The identification of advanced age as a key risk factor in both local and national datasets has direct implications for healthcare resource allocation and underscores the need for targeted protective strategies, including prioritized vaccination and early intervention for older adults. The lack of a significant comorbidity association with hospitalization in our cohort likely reflects limited power; larger studies have identified comorbidities as significant risk factors for severe outcomes [36, 38]. Studies of the early Omicron wave in Taiwan have also found comorbidities to be major risk factors for COVID-19-related mortality and severe disease [9, 10].

This study's strength lies in its comprehensive approach, integrating local clinical data, national epidemiological trends, and genomic surveillance. Limitations include the small, single-center clinical cohort (n = 22), restricting generalizability and statistical power, especially for analyses involving sex, viral load (Ct), comorbidities, vaccination status, antiviral use, and treatment outcomes. Furthermore, the use of targeted S-gene Sanger sequencing (rather than WGS) for this cohort limits our ability to *de novo* detect novel recombinants and relies on matching Spike profiles to known, established lineages. These limitations are common in rapid regional studies, highlighting the need for larger, multi-center collaborations for clinical insights. The GISAID dataset (n = 1782), while valuable for subvariant profiling, is subject to sequencing and submission biases and lacks linked clinical data. Thus, it provides an important but incomplete overview, underscoring the significance of integrative studies that combine local genomic data with detailed clinical outcomes. The observational cohort design and confounding by indication, where 100 % (10/10) of all severe/moderate cases and 67 % (8/12) of mild cases received antivirals, made it impossible to draw definitive conclusions regarding treatment efficacy. Specifically, the lack of an untreated control group within the severe/moderate cohort, combined with the small sample size, precludes any meaningful statistical adjustment or stratification for this confounding. This reflects a common limitation in real-world evidence during emerging infectious disease outbreaks, where randomized controlled trials may be infeasible or delayed, and our dataset lacks granular data on treatment timing or dosage, underscoring the need to interpret antiviral usage patterns as descriptive rather than indicative of efficacy. Changes in national case definitions significantly impacted epidemiological data, complicating temporal trend interpretation and international comparisons of morbidity and mortality. This reflects a broader global challenge, where evolving surveillance strategies and definitions hinder direct comparisons over time and across regions, emphasizing the need for epidemiological analyses to carefully account for such contextual factors. Furthermore, reliance on aggregated public data precluded access to individual-level information, limiting detailed risk factor analyses beyond age. The challenge of accessing and linking comprehensive individual-level national health data, while ensuring privacy, is a global concern that constrains the depth of epidemiological investigations and hampers identification of nuanced risk profiles. Finally, our phylogenetic analysis is focused on genomic epidemiology—i.e., variant classification and tracking—rather than mechanistic molecular evolution. The lack of deeper evolutionary analyses, such as selective pressure (dN/dS) or mutation hotspot investigation, is a limitation of this study's scope. Future research should focus on larger, representative Taiwanese cohorts to elucidate clinical and virologic correlates of emerging Omicron subvariants and vaccine effectiveness. Continued genomic and epidemiological surveillance remains essential to monitor SARS-CoV-2 evolution, inform public health policy, and guide vaccine updates [39–40], especially as the virus transitions toward endemicity. Understanding regional differences in viral transmission and clinical impact is also important.

Conclusions

Taiwan experienced a dynamic evolution of SARS-CoV-2 Omicron subvariants from late 2023 to early 2025, with JN.1 and its descendants emerging as dominant strains, which fueled new infection waves in 2024. Importantly, the interpretation of these epidemiological trends were significantly confounded by changes in case definitions, which created significant statistical artifacts (such as an artificial surge in CFR) that must be carefully distinguished from true changes in viral virulence. While advanced age was not identified as a statistically significant risk factor in our limited local cohort, national-level data also confirmed it remained a key risk factor for hospitalization and mortality, particularly among individuals with chronic comorbidities and low uptake of recent booster doses. These findings provide insight into recent SARS-CoV-2 dynamics in Taiwan and reinforce the ongoing need for integrated genomic and epidemiological surveillance that can contextualize epidemiological metrics against confounding administrative policy changes.

CRediT authorship contribution statement

Conceptualization: L.T.L., J.J.T.; Methodology: C.Y.L., P.C.C., C.H.C., P.C.L., C.Y.T.; Validation: L.T.L., C.J.C., Y.C.L., J.J.T.; Formal analysis: L.T.L., P.C.L., C.Y.T., S.H.L., C.H.L., J.J.T.; Investigation: C.J.C., Y.C.L., P.C.L., J.J.T.; Resources: J.J.T.; Data curation: L.T.L., C.Y.T.; P.C.L., J.J.T.; Visualization: L.T.L.; Supervision: J.J.T.; Funding acquisition: J.J.T.; Writing—original draft: L.T.L., J.J.T.; Writing—review and editing: L.T.L., J.J.T. All authors confirm that they had full access to all the data in the study and take responsibility for its integrity and the accuracy of the analysis. All authors approved the final version for submission.

Ethics approval and consent to participate

The current study was reviewed and approved by the Institutional Review Board of KMUH (approval no. KMUHIRB-E-I-20200013). We obtained written informed consent before sample collection.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Gemini 2.5 Pro (preview), a large language model developed by Google, in the preparation of this manuscript. The AI model contributed to text refinement for clarity and conciseness. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2025.103075.

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