Factors associated with delayed diagnosis of symptomatic adult COVID-19 cases presenting to primary care: a population-wide study during transition from Delta to Omicron BA.1 in Singapore

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Summary

Background During pandemics, avoiding time delay in diagnosing infection is crucial. We evaluated factors associated with delayed diagnosis of symptomatic SARS-CoV-2 infection in a national cohort of adult Singaporeans, during which emergence of the more transmissible Omicron variant shifted pandemic management towards endemicity.

Methods Retrospective cross-sectional study amongst all adult Singaporeans diagnosed with symptomatic SARS-CoV-2 infection during the transition from Delta to Omicron BA.1 (September 2021–February 2022). SARS-CoV-2 testing was fully subsidised and compulsory for all symptomatic individuals presenting at primary care. Results and demographic information were extracted from national databases. Time to diagnosis was defined as days from symptom-onset to diagnosis (date of first positive SARS-CoV-2 test); dichotomising into no delay (≤24 h from symptom-onset) and delay >24 h. Multivariable logistic regression was utilised to assess factors associated with delay >24 h, and association of delay >24 h with progression to severe COVID-19.

Findings Of 149,063 Singaporean adults presenting with symptomatic SARS-CoV-2 infection, 75.9% (113,195/149,063) were diagnosed within 24 h of symptom-onset. On multivariable analysis, female gender, older age (>60 years), Chinese (vs. Malay) ethnicity, socioeconomic status (housing type), primary care characteristics, presentation during Omicron BA.1 (vs. Delta), symptom-onset on Friday/Saturday (vs. Monday), and not having completed a primary vaccination series were independently associated with higher odds of delay >24 h. Delay >24 h was independently associated with severe COVID-19 (adjusted odds-ratio, aOR = 1.45, 95% CI = 1.27–1.65, $p < 0.001$).

Interpretation At-risk populations (unvaccinated, age >60 years) had higher odds of delay in diagnosis. Delay >24 h in diagnosis was independently associated with severe COVID-19.

Funding This study was not grant-funded.

Keywords: SARS-CoV-2; COVID-19; Delay; Diagnosis; Primary care

Introduction

During pandemics, avoiding time delay in diagnosing infection is crucial to better control spread and limit negative health consequences. Studies at the onset of the ongoing coronavirus-disease-2019 (COVID-19) pandemic amply demonstrated that reducing delays in diagnosis substantially mitigated outbreaks by improving efficiency of contact tracing and quarantine, thereby decreasing onward transmission.[1–3] Even as countries transition from pandemic mitigation to endemicity, delays in diagnosis can still limit the potential impact of early treatment and intervention. For

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Research in context

Evidence before this study

While prior studies had examined the factors associated with delays in diagnosis of SARS-CoV-2 infection, all of these studies were conducted at the onset of the pandemic period when testing capacity was reduced and were limited to small cohorts.

Added value of this study

In this study, we utilised data from a high-quality national SARS-CoV-2 testing registry covering an entire population, during a transition in prevailing SARS-CoV-2 variants (Delta to Omicron BA.1). Our findings showed that in the context of widely available free SARS-CoV-2 testing in the primary care setting, 75.9% (113,195/149,063) of cases were diagnosed within 24 h of symptom-onset. Population subgroups at higher risk of severe COVID-19 (age >60 years, unvaccinated individuals) had higher odds of delayed diagnosis (>24 h). Delay >24 h was independently associated with higher odds of progression to severe COVID-19.

Implications of all the available evidence

At-risk populations (unvaccinated, age >60 years) had higher odds of delay, even in the context of widely available subsidised SARS-CoV-2 testing in primary care. Delay >24 h in diagnosis was independently associated with severe COVID-19.

instance, while oral antivirals have demonstrated benefit in reducing COVID-19 severity and risk of subsequent hospitalisation, usage is limited to patients with symptom onset no more than 5 days.[4] Delays in diagnosis impact outcomes of not just COVID-19 but also other common respiratory illnesses with pandemic potential, such as influenza. For example, from surveillance data of patients hospitalised with influenza in the United States, almost two-thirds started antivirals more than 3 days after illness onset,[5] despite greater clinical benefit being derived from earlier initiation of treatment.[6] Identifying factors associated with delayed diagnosis is crucial in formulating strategies to address testing hesitancy during ongoing outbreaks of acute-respiratory-illness (ARI) driven by an emergent respiratory viral pathogen.

Given the importance of testing as a cornerstone of pandemic management, testing hesitancy may affect uptake and subsequent healthcare utilisation.[7] Disparities in COVID-19-related testing uptake and healthcare utilisation have been extensively documented in large population-based studies.[7–9] Previous studies attributed delayed diagnosis in the initial pandemic wave to social determinants of health, such as lower socioeconomic-status (SES)[10] and older age.[11,12] However, the majority of studies that examined determinants of diagnostic delay were conducted earlier in the pandemic period when testing capacity was more limited.[10–12] As such, findings may not reflect the current reality of widely available population-wide rapid diagnostic testing during COVID-19 endemicity.[13] Transition to endemicity and the current prevalence of milder SARS-CoV-2 variants such as the Omicron variant may significantly modify public perceptions regarding care-seeking,[14] contributing to further delays in diagnosis. Additional studies are therefore needed to evaluate determinants associated with delays in diagnosis during the present shift to COVID-19 endemicity. We evaluated factors associated with delayed diagnosis of symptomatic SARS-CoV-2 infection at the primary care level, in a national cohort of adult Singaporeans, during Delta and subsequent transition to Omicron BA.1. The emergence of the more transmissible Omicron variant marked a shift in Singapore's pandemic management strategies from test-and-trace to COVID-19 endemicity.[15]

Methods

Review of pre-existing literature

We searched Pubmed for abstracts of studies examining delays in COVID-19 diagnosis, up to 23rd June 2023, using the following search terms: "delayed diagnosis", "time to diagnosis", "COVID-19". A total of 165 abstracts thus identified were subsequently manually screened for relevancy by two of the co-authors independently. Full references of articles deemed relevant were screened through to identify additional related articles. Four relevant articles were identified; all studies were conducted at onset of the pandemic and limited to small cohorts.[10–12,16] No studies evaluated factors associated with delays in diagnosis of SARS-CoV-2 infection in a nationally representative population over a sustained period of population-wide testing.

Ethics approval

This study was done as part of national public health research under the Infectious Diseases Act, Singapore, to support evaluation of the public health response to COVID-19; hence, separate ethics review by an Institutional Review Board was not required.

Study population, study period and data sources

We conducted a retrospective cross-sectional study amongst all non-hospitalised adult Singaporean citizens/permanent residents aged ≥18 years presenting to primary care with symptomatic SARS-CoV-2 infection over the transition from Delta to initial emergence of Omicron BA.1 in Singapore. The study period was from 18th September 2021 to 18th February 2022. The SARS-CoV-2 Delta variant was first detected in Singapore in

April 2021 and subsequently predominated community transmission (≥90% of circulating strains on genomic surveillance) by September 2021, up to January 2022.[15] Local transmission of Omicron BA.1/2 was first detected on 2 December 2021; Omicron subsequently replaced Delta as the predominant strain by January 2022.[15] From 18th February 2022 onwards, given surging community transmission of Omicron, public health strategies in Singapore shifted away from testing and containment.[17] Over the study period, all Singaporean residents with symptoms of acute-respiratory-illness (ARI) were strongly encouraged via public health messaging to seek consultation with a healthcare provider for clinical assessment and SARS-CoV-2 testing (either polymerase-chain-reaction test, PCR, or rapid-antigen-test, RAT).[18] Testing for SARS-CoV-2 (PCR/RAT) was compulsory for all individuals who presented with ARI symptoms to any healthcare provider, and details of positive cases (including date of symptom onset and date of positive test) were required by law to be notified to our local Ministry of Health (MOH), which maintained national records of all confirmed SARS-CoV-2 infections.[18] It was mandatory to report date of symptom onset for symptomatic COVID-19 cases to MOH, up to mid-February 2022.

For the duration of the study period, SARS-CoV-2 testing (PCR/RAT) was free at all healthcare providers; Singaporeans presenting with ARI symptoms at all public primary care clinics (polyclinics) as well as all Public-Health-Preparedness-Clinics (PHPCs) would pay a subsidised rate of S$5–10 (US$3–8) for consultation and treatment.[18] PHPCs comprise a network of over 1000 private general practitioner (GP) clinics that provide subsidised treatment, investigations and medications for Singaporean citizens/permanent residents during public health emergencies.[18] In Singapore, primary care is provided via private GPs and public polyclinics. The private sector accounts for 80% of primary care visits, while public polyclinics account for 20% of patient load.[19] Primary health care is funded by a mixture of private and public expenditure; pre-pandemic, acute care visits, such as those for ARI symptoms, would generally be paid for out-of-pocket, with government subsidies available at public polyclinics.[19]

Anonymized data, including demographic variables, such as age, sex, ethnic group (Chinese, Malay, Indian, or others), comorbidities and indicators of SES (housing type; staying in public rental flats) were extracted from official databases maintained by our local MOH. In Singapore, housing type is a key indicator of SES; the majority of Singaporeans (≥90%) own their own homes, with public rental flats providing heavily subsidized rentals for the needy who cannot afford to own homes.[20] COVID-19 vaccination status was extracted from MOH's databases. Singapore's national adult COVID-19 vaccination program began on December 30, 2020, and vaccination uptake was high; by 18th September 2021, 82% of the population had already completed a full vaccination regimen.[21]

Study outcomes

Time to diagnosis was defined as number of days from symptom onset to diagnosis (date of first positive SARS-CoV-2 test administered by a healthcare provider). Given that the large majority (≥90%) of patients presented to primary care for diagnosis within 48 h of symptom onset, we further dichotomised cases into no delay (≤24 h from symptom onset) and delay >24 h from symptom onset. We further assessed if delay >24 h was associated with subsequent progression to severe COVID-19 disease. Severe COVID-19 disease was defined as requiring oxygen supplementation, intensive care unit admission, or death, amongst patients hospitalised for COVID-19. Reporting information on COVID-19 hospitalisations and severity of COVID-19 disease to our local MOH was mandatory under the Infectious Diseases Act.[18]

Statistical analysis

Descriptive statistics were presented as median (interquartile range, IQR) and percentage (%) as appropriate. Chi-square test was used to compare proportions (no delay/delay >24 h) on univariate analysis. We used multivariable logistic regression with robust standard errors to assess clinical and sociodemographic variables associated with delay >24 h, using the cluster option to control for potential correlation within residential districts (as defined by group-representation-constituencies, GRCs, which are demarcated by electoral boundaries). As Omicron became the predominant strain by January 2022,[15] we originally classified variant period (Omicron vs. Delta) using 1 January 2022 as a cutoff and included prevailing variant as a covariate in our analyses. However, as a supplementary analysis, we excluded individuals infected during the 6-week transition period (2 December 2021–15 January 2022), thereby stratifying our sample into Delta-only transmission (18th September 2021–1st December 2021) and Omicron-only transmission (16th January 2022–18th February 2022), and examined factors associated with delay >24 h during both periods; the rationale being that attitudes towards diagnosis and testing might have been in flux during the period of transition. As a check for multicollinearity, we examined the variance-inflation-factor (VIF) for the various independent variables; all VIFs were less than 5. Given the right-skewed non-negative nature of our outcome variable (number of days from symptom onset to diagnosis), as an additional sensitivity analysis, we used a multivariable Poisson regression model to assess factors associated with time to diagnosis from symptom onset (days),[16] and explore the consistency of estimates derived earlier from logistic regression. Robust standard errors were used in order to

control for mild violation of underlying assumptions. We subsequently assessed the fit of the Poisson model to the underlying data using the goodness-of-fit chi-square test; the result was not statistically significant ($p = 1.00$), suggesting a reasonable fit to the underlying data. Finally, we used multivariable logistic regression to assess if delay >24 h in diagnosis was associated with subsequent progression to severe COVID-19 disease, while controlling for other clinical and sociodemographic factors. Our analysis was performed using Stata version 17.0 (StataCorp LP, College Station, TX, USA); STATA codes for multivariable models are included in the Supplementary Material. All significance tests were two-tailed, and a p value of less than 0.05 was considered statistically significant.

Role of funding source
This study was not grant-funded.

Results
During the study period, a total of 149,063 Singapore adults aged ≥18 years were diagnosed with symptomatic SARS-CoV-2 infection at primary care. Of these, the majority (75.9%, 113,195/149,063) were diagnosed within 24 h of symptom onset, with 91.7% (136,690/149,063) diagnosed within 48 h of symptom onset. The majority of patients (90.3%, 134,652/149,063) were diagnosed at PHPCs, with smaller numbers diagnosed at polyclinics (N = 5093) and at private GPs not part of the PHPC network (N = 9318). Around 4.2% (6189/149,063) of adults who were first diagnosed with symptomatic SARS-CoV-2 infection at primary care were subsequently hospitalised; 0.70% (1037/149,063) subsequently progressed to severe COVID-19 disease.

On univariate analysis, female gender, older age (>60 years), Chinese (majority) ethnicity, staying in 1–2 room public housing or private housing (vs. 5-room public housing), presenting to a public polyclinic (vs. a private GP clinic), presenting to a clinic that did not offer telemedicine or 24-h services, having higher comorbidity burden, immunocompromised status, presentation during the Omicron BA.1 period (vs. Delta), symptom onset on Friday/Saturday (vs. Monday), and not having completed a primary vaccination series were all associated with greater odds of delay >24 h in diagnosis of symptomatic SARS-CoV-2 infection at primary care (Table 1). On multivariable analysis, female gender, older age (>60 years), Chinese (vs. Malay) ethnicity, staying in 1–2 room public housing or private housing (vs. 5-room public housing), presenting to a public polyclinic (vs. a private GP clinic), presenting to a clinic that did not offer telemedicine or 24-h services, presentation during the Omicron BA.1 period (vs. Delta), symptom onset on Friday/Saturday (vs. Monday), and not having completed a primary vaccination series were independently associated with higher odds of delay >24 h in diagnosis at primary care (Table 2). When analysis was stratified into Delta-only and Omicron-only transmission waves, estimates were fairly similar; with the exception being that during the Omicron period, differences in odds of delay >24 h by age and housing type (SES) were no longer statistically significant (Supplementary Table S1). Estimates derived using Poisson regression of time-to-diagnosis were fairly consistent (Supplementary Table S2). On multivariable logistic regression, delay >24 h was independently associated with subsequent progression to severe COVID-19 (adjusted-odds-ratio, aOR = 1.45, 95% CI = 1.27–1.65, $p < 0.001$), after controlling for other sociodemographic and clinical factors (Table 3).

Discussion
Amongst adult Singaporeans, during a shift from Delta to Omicron-predominant transmission, 75.9% (113,195/149,063) of COVID-19 cases were diagnosed within 24 h of symptom-onset, in the context of widely available free SARS-CoV-2 testing in the primary care setting. In comparison, during the early phase of the pandemic, amongst adult Chinese in Shanxi, it took on average 2.3 days to seek healthcare after symptom onset and another 5.6 days to reach the diagnosis of COVID-19[11]; while amongst adult Okinawans, the median number of days from onset to diagnosis was 3 days.[12] Differences in testing hesitancy and delayed diagnosis at primary care may arise from pre-existing social determinants of health, factors affecting access to primary care, or individual demographic factors affecting initial care seeking.[8] Amongst adult Singaporean residents diagnosed with symptomatic SARS-CoV-2 infection at primary care during the transition from Delta to the Omicron variant, demographic and clinical factors associated with poorer COVID-19 outcomes, such as unvaccinated/partially vaccinated status and older age (>60 years), had greater odds of delay in diagnosis at primary care; older adults (>60 years), for instance, had higher odds of delay (aOR = 1.29, 95% CI = 1.26–1.37) compared to those 30 years and younger. These differences, however, did not persist into the Omicron period. In Singapore, COVID-19 vaccination uptake is high: more than 90% of the adult population completed vaccination with the primary series and 77% received at least one booster dose by June 2022 under the national vaccination program.[22] Factors associated with COVID-19 vaccination hesitancy, such as reduced perceived threat from COVID-19,[23] may also potentially contribute to testing hesitancy and delayed diagnosis, and should be addressed in tandem when crafting public health messaging. Delayed diagnosis in older age groups has also been reported in other studies from earlier pandemic waves in other urbanised Asian populations.[11,12] For instance, amongst Chinese adults in Shanxi, those aged 60 and above took 2.5 more days on

Sociodemographic and clinical factors	Delay (>24 h) from symptom onset to diagnosis of SARS-CoV-2 infection at primary care, N (%)
Demographic factors	
Gender	
Female	16,368/65,231 (25.0)
Male	19,500/83,832 (23.3)
Age distribution, years	
18–30 years	5604/25,770 (21.8)
31–60 years	19,834/86,329 (23.0)
>60 years	10,430/36,964 (28.2)
Ethnicity	
Chinese	23,350/93,656 (24.9)
Malay	4796/22,336 (21.4)
Indian	5120/22,054 (23.2)
Others[a]	2602/10,987 (23.7)
Socioeconomic factors	
Housing type	
5-room/executive condominium-type public housing	7501/31,631 (23.7)
1–2 room public housing	1802/6967 (25.9)
3–4 room public housing	18,396/78,519 (23.4)
Private housing	8169/31,946 (25.6)
Staying in public rental housing	
Owner-occupied housing	34,686/144,361 (24.0)
Public rental housing	1182/4702 (25.1)
Primary care characteristics	
Primary care provider	
Public polyclinic	2156/5093 (42.3)
Private general practitioner clinic part of the PHPC network	31,287/134,652 (23.2)
Private general practitioner clinic not part of the PHPC network	2425/9318 (26.2)
Clinic offers 24-h services	
No	34,813/138,333 (25.2)
Yes	1055/10,730 (9.8)
Clinic offers telemedicine services	
No	33,661/137,322 (24.5)
Yes	2207/11,741 (18.8)
Clinical factors	
Comorbidity burden (Charlson Comorbidity Index, CCMI)	
No comorbidities (CCMI = 0)	29,571/125,846 (23.5)
Mild comorbidities (CCMI 1–3)	4550/16,801 (27.1)
Moderate comorbidity burden (CCMI 3–4)	1191/4402 (27.1)
Severe comorbidity burden (CCMI ≥5)	556/2014 (27.6)
Immunocompromised[b]	
No	34,443/143,854 (23.9)
Yes	1425/4209 (33.9)
Infection factors	
SARS-CoV-2 variant in circulation	
Delta	25,693/110,507 (22.2)
Omicron BA.1	10,175/38,556 (26.4)
Day of symptom onset	
Monday	5686/24,936 (22.8)
Tuesday	4763/21,388 (22.3)
Wednesday	4777/20,770 (23.0)
Thursday	4122/19,954 (20.7)
Friday	4949/18.581 (26.6)

(Table 1 continues on next page)

Sociodemographic and clinical factors	Delay (>24 h) from symptom onset to diagnosis of SARS-CoV-2 infection at primary care, N (%)
(Continued from previous page)	
Saturday	6765/19,292 (35.1)
Sunday	4806/24,142 (19.9)
COVID-19 vaccination status[c]	
Did not complete primary vaccination series	108/352 (30.7)
Completed primary vaccination series	10,072/43,102 (23.4)
Received booster dose in addition to primary vaccination series	25,688/105,609 (24.3)

[a]Includes individuals of other ethnicities or mixed ethnicities. [b]Immunocompromised status was defined as: presence of solid malignancy, hematologic malignancy, rheumatologic or inflammatory disorders, other intrinsic immune condition or immunodeficiency, or organ or stem cell transplant. [c]COVID-19 vaccination was classified as follows: had not completed a primary vaccination series (eg, <2 doses of mRNA COVID-19 vaccines); completed a primary vaccination series (defined as 2 vaccine doses, in the case of mRNA COVID-19 vaccines); received booster dose (defined as 3 or more vaccine doses, in the case of mRNA COVID-19 vaccines).

Table 1: **Sociodemographic and clinical factors associated on univariate analysis with delay (>24 h) from symptom onset to diagnosis of SARS-CoV-2 infection at primary care, amongst adult Singaporeans presenting during Delta and Omicron BA.1 waves (N = 149,063).**

average to visit a doctor for diagnosis of COVID-19, compared to those younger than 30 years old[11]; while amongst Okinawan adults, patients in their 60s reported significantly more time from symptom onset to diagnosis (hazard-ratio = 0.88; 95% CI = 0.81–0.96).[12] Improving access and prioritising outreach for testing amongst unvaccinated/partially vaccinated older individuals at high risk of serious illness could potentially reduce COVID-19 associated morbidity and mortality.

Characteristics of primary care, such as accessibility and availability, are also likely to influence diagnostic delay during an ongoing pandemic. We found that diagnosis was delayed for those with the onset of symptoms just prior to the weekend, as compared to symptom onset on a Monday (eg, symptom onset on Friday: aOR = 1.26, 95% CI = 1.15–1.36; symptom onset on Saturday: aOR = 1.93, 95% CI = 1.75–2.12); these findings persisted through both Delta and Omicron periods. Similarly, amongst Okinawan adults, significantly more time from symptom onset to diagnosis was observed in those with symptom onset on Sundays/national holidays, compared to those with symptom onset on weekdays (hazard-ratio = 0.90, 95% CI = 0.85–0.96).[12] Many medical clinics are closed on weekends; if symptoms are mild, many people may choose to avoid testing at crowded 24-h emergency departments, and may test only later in the week. This is of concern during a pandemic, however, as the duration of social contact is higher on weekends than on weekdays.[24] Delayed testing on weekends may thus contribute to greater risk of transmission. During the COVID-19 pandemic in Singapore, PHPCs were encouraged to open on weekends and after-hours on weekdays; additionally, community-based quick test centres were opened on weekends to test people with ARI symptoms, in order to facilitate prompt testing.[25] Such services can potentially be scaled up during future pandemics in order to ensure prompt testing and minimise diagnostic delay.

Staying in both 1–2 room public housing (lower SES) and staying in private housing (higher SES) had greater odds of delayed diagnosis during the Delta period; however, these differences did not persist into the subsequent Omicron wave. The majority of Singaporeans (≥85%) stay in public housing,[21] with housing type considered a key indicator of SES. Studies in Hong Kong, another densely populated urbanised society, demonstrated that staying in public rental housing was associated with longer time to diagnosis in the first pandemic wave.[10] Similarly, the socioeconomic gradient in time to diagnosis observed in Hong Kong during the early phase of the pandemic diminished in later waves, coinciding with the provision of free testing on a population-wide basis.[10] However, other studies have shown that disparities in SARS-CoV-2 testing uptake may persist despite deliberate efforts to address pre-pandemic inequalities, including provision of subsidised testing.[9] While higher-SES strata may possibly present later to care because of increased accessibility to self-administered SARS-CoV-2 testing, delayed testing amongst lower-SES strata, even with fully subsidised testing, is of concern. Pre-pandemic, only a minority of lower-income Singaporean residents expressed a preference to approach their primary care practitioner as their first choice for medical consultation and care, largely due to cost.[26] Although free SARS-CoV-2 testing and heavily subsidised consultation/treatment was available at healthcare providers over the pandemic period, testing disparities may persist due to individuals' past familiarity and frustrations with the healthcare system influencing their initial care-seeking behaviour.[8,9] Targeted efforts are needed to overcome personal, community and test-related barriers in a contextually sensitive manner in order to improve testing uptake among underserved communities.

The limitations of our study are as follows: Time from symptom-onset to confirmation of SARS-CoV-2 infection was based on PCR/RAT performed by

Sociodemographic and clinical factors	Multivariable logistic regression of factors associated with delay (>24 h) from symptom onset to diagnosis of SARS-CoV-2 infection at primary care, amongst adults aged ≥18 years[a]	
	Adjusted odds-ratio, aOR [95% CI]	p-value
Demographic factors		
Gender		
Female	1.00 (ref)	
Male	0.92 [0.89, 0.94]	<0.001
Age distribution, years		
18–30 years	1.00 (ref)	
31–60 years	1.05 [1.01, 1.09]	0.016
>60 years	1.29 [1.26, 1.37]	<0.001
Ethnicity		
Chinese	1.00 (ref)	
Malay	0.84 [0.79, 0.89]	<0.001
Indian	0.96 [0.92, 1.00]	0.081
Others[b]	0.98 [0.91, 1.05]	0.508
Socioeconomic factors		
Housing type		
5-room/executive condominium-type public housing	1.00 (ref)	
1–2 room public housing	1.13 [0.98, 1.30]	0.049
3–4 room public housing	1.00 [0.95, 1.05]	0.887
Private housing	1.18 [1.10, 1.26]	<0.001
Primary care characteristics		
Primary care provider		
Public polyclinic	1.00 (ref)	
Private general practitioner clinic part of the PHPC network	0.43 [0.36, 0.52]	<0.001
Private general practitioner clinic not part of the PHPC network	0.46 [0.31, 0.69]	<0.001
Clinic offers 24-h services		
No	1.00 (ref)	
Yes	0.34 [0.21, 0.59]	<0.001
Clinic offers telemedicine services		
No	1.00 (ref)	
Yes	0.79 [0.67, 0.93]	0.005
Clinical factors		
SARS-CoV-2 variant in circulation		
Delta	1.00 (ref)	
Omicron BA.1	1.08 [1.01, 1.16]	0.022
Day of symptom onset		
Monday	1.00 (ref)	
Tuesday	0.97 [0.92, 1.01]	0.127
Wednesday	1.01 [0.94, 1.09]	0.613
Thursday	0.89 [0.85, 0.93]	0.001
Friday	1.26 [1.15, 1.36]	<0.001
Saturday	1.93 [1.75, 2.12]	<0.001
Sunday	0.84 [0.77, 0.92]	<0.001
COVID-19 vaccination status[c]		
Did not complete primary vaccination series	1.00 (ref)	
Completed primary vaccination series	0.72 [0.56, 0.92]	0.008
Received booster dose in addition to primary vaccination series	0.71 [0.55, 0.90]	0.006

[a]Adjusted for: gender, age, ethnicity, housing type, public rental housing, day of symptom onset, primary care provider and characteristics, COVID-19 vaccination status, comorbidity burden, immunocompromised status; controlling for clustering by geographical location (group representation constituency, GRC). [b]Includes individuals of other ethnicities or mixed ethnicities. [c]COVID-19 vaccination was classified as follows: had not completed a primary vaccination series (eg, <2 doses of mRNA COVID-19 vaccines); completed a primary vaccination series (defined as 2 vaccine doses, in the case of mRNA COVID-19 vaccines); received booster dose (defined as 3 or more vaccine doses, in the case of mRNA COVID-19 vaccines).

Table 2: **Sociodemographic and clinical factors associated on multivariable analysis with delay (>24 h) from symptom onset to diagnosis at primary care, amongst adult Singaporeans (aged ≥18 years) presenting with symptomatic SARS-CoV-2 infection during Delta and Omicron BA.1 waves (N = 149,063).**

Sociodemographic and clinical factors	Multivariable logistic regression of factors associated with progression to severe COVID-19 disease[c]	
	Adjusted odds ratio, aOR (95% CI)	p-value
Delay in diagnosis at primary care		
Delay (>24 h) from symptom onset to diagnosis	1.45 [1.27, 1.65]	<0.001
Demographic factors		
Gender		
Female	1.00 (ref)	
Male	1.20 [1.05, 1.36]	0.005
Age distribution, years		
18–30 years	1.00 (ref)	
31–60 years	15.51 [6.40, 37.57]	<0.001
>60 years	61.69 [25.47, 149.44]	<0.001
Ethnicity		
Chinese	1.00 (ref)	
Malay	0.83 [0.69, 0.99]	0.048
Indian	0.29 [0.21, 0.40]	<0.001
Others[a]	0.56 [0.37, 0.85]	0.007
Clinical factors		
SARS-CoV-2 variant		
Delta	1.00 (ref)	
Omicron BA.1/2	0.24 [0.20, 0.28]	<0.001
COVID-19 vaccination status[b]		
Did not complete primary vaccination series	1.00 (ref)	
Completed primary vaccination series	0.07 [0.04, 0.12]	<0.001
Received booster dose in addition to primary vaccination series	0.19 [0.11, 0.31]	<0.001
Comorbidity burden (Charlson Comorbidity Index, CCMI)		
No comorbidities (CCMI = 0)	1.00 (ref)	
Mild comorbidities (CCMI 1–3)	2.55 [2.19, 2.98]	<0.001
Moderate comorbidity burden (CCMI 3–4)	3.69 [2.98, 4.57]	<0.001
Severe comorbidity burden (CCMI ≥5)	7.04 [5.56, 8.92]	<0.001

[a]Includes individuals of other ethnicities or mixed ethnicities. [b]COVID-19 vaccination was classified as follows: had not completed a primary vaccination series (eg, <2 doses of mRNA COVID-19 vaccines); completed a primary vaccination series (defined as 2 vaccine doses, in the case of mRNA COVID-19 vaccines); received booster dose (defined as 3 or more vaccine doses, in the case of mRNA COVID-19 vaccines). [c]Adjusted for: delay in diagnosis at primary care, gender, age, ethnicity, SARS-CoV-2 variant, vaccination status, comorbidity burden in multivariable logistic regression model.

Table 3: **Sociodemographic and clinical factors, including delay (>24 h) in diagnosis at primary care, associated on multivariable analysis with subsequent progression to severe COVID-19 disease amongst adult Singaporeans (N = 149,063).**

healthcare providers; while healthcare providers were mandated to report results of COVID-19 testing, results of self-administered RAT were not included in our national database. However, it was likely that healthcare-associated consults would tend towards cases with more significant symptoms. Residual confounding from other unmeasured factors affecting individual COVID-19 risk that may have potentially influenced testing decisions could not be fully excluded. Finally, this study was conducted during a shift in Singapore's pandemic management strategies from test-and-trace to COVID-19 endemicity; predominant transmission of milder SARS-CoV-2 variants may affect attitudes towards COVID-19 testing and thereby influence testing uptake, affecting generalisability.

In conclusion, in a national cohort of adult Singaporeans presenting to primary care for symptomatic SARS-CoV-2 infection during transition from Delta to the Omicron variant, symptom onset prior to the weekend (vs. Monday), staying in 1–2 room public housing (lower SES), not completing a primary COVID-19 vaccination series, and older age (age >60 years) had greater odds of delay >24 h in diagnosis of symptomatic COVID-19 infection at primary care. Delay >24 h in diagnosis was independently associated with progression to severe COVID-19, highlighting its clinical significance. Delayed diagnosis during an ongoing pandemic increases the risk of onward transmission[1–3] and limits the impact of early treatment and intervention.

Contributors

RYT and LEW contributed to literature search and writing of the manuscript. BW, RL, CLL, JT, and KBT contributed to critical review and editing of the manuscript. LEW and KBT provided supervision. KBT,

LEW, and RYT contributed to study design, data collection, data analysis and editing of the manuscript. All authors had full access to all the data in the study and take responsibility for the decision to submit for publication. LEW and RYT directly accessed and verified the underlying data reported in the manuscript.

Data sharing statement

The databases with individual-level information used for this study are not publicly available due to personal data protection. Deidentified data can be made available for research, subject to approval by the Ministry of Health of Singapore. All inquiries should be sent to the corresponding author.

Declaration of interests

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100919.

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