ORIGINAL ARTICLE

Clinical severity of COVID-19 with omicron variant predominance in relation to vaccination status, age, comorbidities- a single center in Selangor, Malaysia

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ABSTRACT

Introduction: Recently, the rapid surge of reported COVID-19 cases attributed to the Omicron variant of severe acute respiratory syndrome coronavirus (SARS-CoV-2) created an immediate concern across nations. Local information pertaining to the new variant of concern (VOC) is lacking. We aimed to determine the clinical characteristics of COVID-19 during a period of Omicron prevalence among patients hospitalised from February 1 to 21, 2022 at Sungai Buloh Hospital and to estimate the risks of disease progression presumably caused by this variant in association with gender, age, comorbidity, and vaccination status.

Materials and Methods: In this retrospective, single-centered, retrospective cohort study, all hospitalised adults with laboratory-confirmed COVID-19, aged 18 and above, were recruited from February 1 to 21, 2022. Clinical characteristics, investigations, and outcomes were assessed.

Results: A total of 2279 patients aged 18 years and above with laboratory-proven COVID-19 were recruited and analysed, excluding 32 patients owing to incomplete data. Majority of the study population had a mean age of 41.8 ± 17.7, was female-predominant (1329/2279, 58.6%), had completed a primary series of vaccination with a booster (1103/2279, 48.4%), and had no underlying medical conditions (1529/2279, 67.4%). The risk of COVID-19-related disease progression was significantly lower in hospitalised patients under the age of 50 who were female, had no comorbidity, and had completed two doses of the primary series with or without a booster. [respectively, OR 7.94 (95% CI 6.16, 10.23); 1.68 (1.34, 2,12); 2.44 (1.85, 3.22); 2.56 (1.65, 3.97), *p*< 0.001].

Conclusion: During the period of Omicron prevalence, a favourable outcome of COVID-19 was strongly associated with female gender, age below 50, a comorbidity-free condition, and having completed immunization. With this new observation, it could help improve public health planning and clinical management in response to the emergence of the latest VOC.

KEYWORDS:
Age, comorbidity, COVID-19, Omicron, severity, vaccination status

INTRODUCTION

Malaysia first reported COVID-19 cases on January 25, 2020[1] and has suffered great losses caused by COVID-19 pandemics up till now. The emergence of the alpha, beta, and delta severe acute respiratory syndrome coronavirus (SARS-CoV-2) variants of concern (VOCs) had previously been linked to new waves of infections that spread globally and resulted in high morbidity and mortality. The B.1.1.529 variant, better known as Omicron, has emerged as a new strain, first detected in South Africa on November 25, 2021.[2] The World Health Organization (WHO) declared it as the fifth variant of concern on November 26, 2021.[3] The presence of 37 mutations in the spike protein enhances the immune evasion, giving an advantage of greater infectivity compared with previous variants.[4,5] From January 24 to February 7, 2022, the main proportion of COVID-19 variants in Malaysia was predominantly Omicron (737/802, 92%) followed by Delta (65/802, 8%) (6). Subsequently, from February 7 to 21, 2022, the Omicron variant (1211/1231, 99%) gradually replaced Delta (20/1231, 1.6%).[6] On February 7, 2022, the Ministry of Health (MOH) declared that the new Omicron had replaced the Delta as the dominant strain in Malaysia.[7] In real-world conditions, the substantial surge of COVID-19 cases during the Omicron-variant encounter is straining the healthcare system. However, recent studies from the UK[8], Canada[9], South Africa[10,11], USA[12], and Sweden[13] described that the Omicron variant, though wildly transmissible, appeared less severe and deadly than the Delta variant in various age groups. Wolter et al. reported that the immunisation programme had significantly reduced the odds of hospital admission and severe disease for patients infected with the Omicron SARS-CoV-2 VOC compared with other SARS-CoV-2 variants during the same period, although reduced severity could be due to past infection.[10,14] To date, no local data was available to clearly delineate the clinical characteristics of the Omicron variant.

To guide the public health planning and response during the period of Omicron prevalence, we sought to study the clinical characteristics of COVID-19; to monitor the risks of hospitalised patients, according to age, sex , comorbidities, and vaccination status.

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MATERIALS AND METHODS

We conducted a retrospective cohort study of adults aged 18 and above who were hospitalised according to the admission criteria (Table I)[15], from February 1 to 21, 2022, during the period of near-universal spread of the Omicron variant in Malaysia, with laboratory-confirmed SARS-CoV-2 infection. During the period of study, Sungai Buloh Hospital was assigned as the primary referral hospital for COVID-19 in the Klang Valley. Cases were retrospectively followed up closely to February 21, 2022. However, cases were excluded if data was invalid or missing; or if subjects were pregnant. We linked data from two main sources: 1. Demographic and clinical data that were retrieved from clinical case notes recorded in electronic datasets of Sungai Buloh Hospital. 2. Vaccination data was obtained from the Malaysia Vaccine Administration System (MyVAS).

Definitions

SARS-CoV2 infection was defined as an individual who was tested positive using either a nasopharyngeal swab (NPS) or oropharyngeal swab (OPS) of rtPCR test for COVID-19, NPS COVID-19 GeneXpert or saliva/NPS RTK Ag for COVID-19.[15] Based on the COVID-19 Management Guideline by the Ministry of Health (Malaysia), each COVID-19 case was classified according to disease severity: stage I (mild)- "asymptomatic", stage II (mild-moderate)- "symptomatic without pneumonia", stage III (moderate)- "pneumonia without hypoxia", stage IV (moderate-severe)- "pneumonia requiring oxygen therapy", stage V (severe)- "critically ill".[15] All confirmed cases would be hospitalised if they fulfilled the admission criteria incorporated by the Ministry of Health, Malaysia.[15] Co-morbidity was described as one or more of the following conditions: diabetes mellitus, chronic cardiac disease, peripheral vascular disease, chronic renal disease, chronic pulmonary disease, malignancy, HIV, chronic liver disease, and stroke.[16,17] Individuals were considered as 1) not fully vaccinated, either they had not been vaccinated (unvaccinated) at all or only one dose of the primary series had been received (partially vaccinated) 2) fully vaccinated if two doses of primary series were administered, including Pfizer-BioNTech (Comirnaty®), Oxford-AstraZeneca (ChAdOx1-S ®) and Sinovac Biotech 3) up-to-date if one booster was received on top of two doses of primary series.[18-22] Cytokine release syndrome is defined as a systemic inflammatory response involving rapidly progressive pneumonitis requiring oxygen supply, with or without multi-organ failure.

Statistical analysis

Sociodemographic data, clinical characteristics, laboratory results, and clinical outcomes were analysed with SPSS version 26. Continuous variables were describe it as standard deviation, SD and interquartile range, IQR, whereas categorical variables as frequency and percentage. Group differences for numerical variables were analysed by using the Students' unpaired t test or Mann-Whitney test; whereas for categorical variables by using Chi-square or Fisher's exact test. The risk estimation was determined by using binomial logistic regression.

RESULTS

From February 1 to 21, 2022, about 81,738 Klang Valley residents aged 18 and above were diagnosed with COVID-19, of whom were 55319 (67.7%) patients aged 18–39, 20,360 (24.9%) aged 40–59, and 6059 (11%) aged 60 and above. Of the total patients, 2311 (2.8%) patients were hospitalised at Sungai Buloh Hospital. There were 32 hospitalised cases being excluded owing to incomplete data collection as they were still receiving inpatient care at our centre. The admission rate was higher in the elderly age group [447/6059 (7.3%)] compared with the middle age group [589/20360 (2.9%)] and the younger age group [1233/55319 (2.2%)].

Among 2269 hospitalised patients, the mean age was 41.8 (SD 17.7) [male: 44 (SD 18), female: 40 (17)]. The majority of hospitalised patients were female (1329/2279, 58.6%), of whom 779/1329 (58.3%) were aged 18–39 years old, 320/1329 (24.1%) aged 40–59, and 230/1329 (17.3%) aged 60 and above; whereas there were 940/2269 (41.4%) male patients who were hospitalised, of whom 454 (48.3%) were aged 18–39, 269 (28.6%) aged 40–59, and 217 (23.1%) aged 60 and above ($p < 0.001$). Of 2269 patients, 1529 (67.4%) had no medical conditions, 476 (21%) had at least one comorbidity, and 264 (11.6%) had two or more comorbidities. Of 1529 patients without coexisting illnesses, 1020 (66.7%) were young people aged 18–39. Half of the patients having two or more health conditions were the elderly (135/264, 51.1%). Of 2269 patients, 1103 (48.4%) had completed the primary series with one booster, 1050 (46.1%) received two doses of the primary series, 14 (0.6%) received only one dose of the primary series, and 102 (4.5%) were not vaccinated yet.

Table II illustrates the severity of disease among the study population in the inpatient setting, based on gender, age category, and the presence of comorbidities, vaccination status. Among 2269 hospitalised patients, 1919 (84.6%) presented with a mild-moderate degree of COVID-19 severity with no disease progression, of whom the majority were young (1173, 61.1%), female (1162, 60.6%) with no comorbidities (1377, 71.8%) and with the administration of a COVID-19 vaccine booster in addition to the primary series (988, 51.5%). Whereas, 350/2269 (15.4%) experienced COVID-19 disease progression, either at presentation or later during hospitalization, of whom the majority were male (183, 52.3%), elderly (185, 52.9%), and with at least one comorbidity (198, 56.6%). In accordance with the vaccination status, the proportion of patients who experienced COVID-19 disease progression was found to be higher among those with incomplete vaccination (36/116, 31%) compared with those who had completed the primary series without a booster shot (199/1050, 19%) and with a booster shot (115/1103, 10.4%).

Table III depicts the odds ratio of risk estimators in association with the disease severity of COVID-19 infection. Female gender, age less than 50 years old, absence of comorbidity, and completion of at least two doses of the primary series were found to be favourable predictors of milder COVID-19 disease. In constrast, the elderly group (age of 60 and above) and the hospitalised patients with at least two comorbidities and more, were at greater risk of experiencing disease progression of COVID-19 pneumonia,

Table I: The admission criteria for patients with the laboratory-confirmed diagnosis of COVID-19.[15]

Criteria for hospital admission of confirmed COVID-19 cases
1. Patients with the COVID-19 infection categorised as 3 to 5
2. Those found to be unstable with warning signs* after evaluation in COVID-19 assessment centres
3. Individuals with comorbidity that is uncontrolled, such as diabetic ketoacidosis, hypertensive emergency, unstable angina etc
4. There is no alternative outpatient dialysis for patients with underlying end-stage renal failure (ESRF) on regular dialysis, though the COVID-19 severity is mild or categorised 1 to 2.
5. Individuals who are immunocompromised**
6. Pregnant mothers in category 2 and higher
7. Pregnant mothers with a BMI of ≥35 kg/m^2 at booking
8. Pregnant mothers who are not fully vaccinated and have medical/obstetrics morbidities, regardless of the disease severity of COVID-19
9. Individuals who are unsuitable to be managed in an outpatient setting while on home quarantine

* Identified warning signs are protracted or worsening symptoms (including persistent cough, angina pectoris, malaise, pyrexia, gastrointestinal losses, anorexia, dyspnoea) and signs (such as confusion, reduced urine output, cyanosis, and oxygen saturation of less than 95%).

** Include solid or bone marrow transplant recipients, people with cancer undergoing active chemotherapy, cancers of the blood and bone marrow, primary immunodeficiency, HIV infected with low CD4 count and not on suppressive ART therapy, splenectomised individuals, on prolonged corticosteroids or other immunosuppressive agents

Table II: The proportion of patients hospitalised for COVID-19 from February 1 to 21, 2022 in relation to age group, comorbidities, vaccination status, and degree of COVID-19 severity

	CAT 1–3 at presentation, without disease progression N=1919		CAT 1–3 at presentation, with disease progression N=61		CAT 4–5 at presentation N=289		Total	*p* value
	n	%	n	%	n	%		
Gender								
Male	757	80.5	31	3.3	152	16.2	940	
Female	1162	87.4	30	2.3	137	10.3	1329	< 0.01
Age group								
18–39	1173	95.1	7	0.6	53	4.3	1233	
40–59	484	82.2	17	2.9	88	14.9	589	
≥ 60	262	58.6	37	8.3	148	33.1	447	< 0.01
Comorbidities								
0	1377	90.1	22	1.4	130	8.5	1529	
1	375	78.8	18	3.8	83	17.4	476	
≥ 2	167	63.3	21	8	76	28.8	264	< 0.01
Vaccination								
Up-to-dated	988	89.6	28	2.5	87	7.9	1103	
Fully vaccinated	851	81	27	2.6	172	16.4	1050	
Not fully vaccinated	80	69	6	5.2	30	25.9	116	< 0.01

with OR 3.26 (95% CI 2.45, 4.32) and OR 5.26 (95% CI 3.89, 7.11), respectively ($p < 0.001$).

DISCUSSION

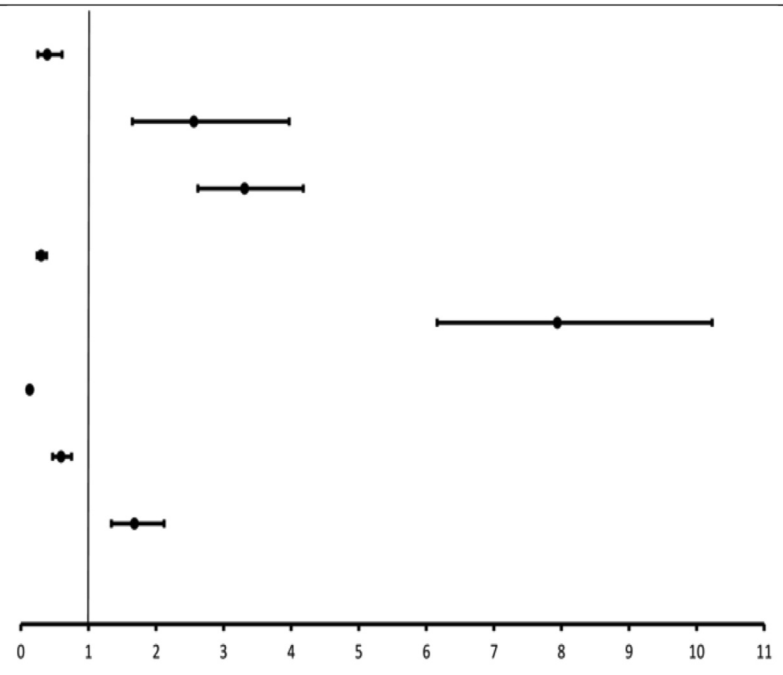
From February 1 to 21, 2022, during which Omicron appeared as the predominant circulating variant across the globe, we observed that a majority of hospitalised patients had not experienced COVID-19 associated severe deterioration. Consistent with earlier studies,[8-10,23,24] hospitalizations during the period of Omicron prevalence were strongly associated with a lower chance of ICU admission, mechanical ventilation, and mortality, compared with the Delta-variant encounter. As reported in the UK, the Omicron cases had a nearly 50% lower risk of hospitalisation and mortality than the Delta cases.[25]

Interestingly, there is evidence stating that the immune effect observed in Delta cases was less than that found in Omicron cases.[10,14] Recent studies suggested a paradigm shift in Omicron-variant tropism towards the upper respiratory tract, in comparison to previous VOCs including Delta and wild type, that had marked tropism for the lower respiratory tract.[26] Even though the Omicron mutations may increase transmissibility as a result of immune escape,[27] they lack the ability to replicate effectively in the lower respiratory tracts, sparing the lung parenchymal tissue and thus not causing severe disease when compared to the Delta variant.[28] Supported by one animal model,[28] reduced pathogenicity in the Omicron variant was observed, resulting in less severe disease involving lower respiratory tracts.

Gender differences are recognised as risk estimators impacting COVID-19 severity. It was reported that the morbidity and mortality rates were significantly higher among males compared with females. Interestingly, the crucial reason behind this observation is presumably related to immune response, hormonal differences, behavioural attitudes, and inflammatory markers.[29] Studies have shown that feminine hormones promote an appropriate immune response to COVID-19 infection and vaccines. Besides, there is a strong association between oestrogen and suppressed

Table III: The odd ratio of age groups, gender, comorbidities, and vaccination status in association with the disease severity of COVID-19

Factor	Predictors towards disease severity of COVID-19	OR (95% CI)	*p* value
Fully vaccinated status		0.39 (0.25, 0.61)	< 0.001
Unvaccinated status		2.56 (1.65, 3.97)	< 0.001
Presence of comorbidities		3.31 (2.62, 4.18)	< 0.001
Comorbidities free		0.30 (0.24, 0.38)	< 0.001
Age > 50		7.94 (6.16, 10.23)	< 0.001
Age < 50		0.13 (0.098, 0.16)	< 0.001
Female		0.595 (0.47, 0.75)	< 0.001
Male		1.68 (1.34, 2.12)	< 0.001



expression of angiotensin-converting enzyme-2 (ACE2) receptors, which are fundamental components of SARS-CoV-2 receptors as the keys to unlocking the doors of host target cells.[30,31] On the other hand, androgens enhance the gain entry of SARS-CoV-2 into host cells via ACE2 receptors, by upregulating the expression of transmembrane protease, serine (TMPRSS2) genes,[32] thus leading to increased susceptibility of males towards COVID-19 infection. Besides, men generally had a higher prevalence of high-risk exposures, for instance, smoking and alcohol consumption.

In line with other studies,[13] the risks of severe disease caused by Omicron variants were significantly higher in unvaccinated individuals aged 50 and older, especially those with multiple comorbidities. In our study, younger individuals without comorbidities barely reported severe complications caused by COVID-19. It is well-known that the risks of life-threatening conditions caused by COVID-19 increase with age, with older individuals being at higher stakes.[33] Up to 80% of COVID-19-related deaths occurred among individuals aged 65 and above, and they were 97 times more likely to die compared with individuals aged 18–29 years.[34] Furthermore, chronic illnesses are well known as the leading cause of mortality and morbidity in COVID-19 infection.[35]

In our study, there was a trend of having higher incidence and hospitalisation rate ratios among COVID-19 patients who had yet to complete their primary series of vaccinations in contrast to those who were fully vaccinated, with or without a booster. In line with one study conducted by Danza et al., the COVID-19 incidence and admission rates in Los Angeles County among unvaccinated patients were 3.6 and 23 times, respectively, higher than those who were fully vaccinated.[12] Furthermore, recent studies found that any individual who received an effective COVID-19 immunisation programme after a booster remains significantly protected against severe damage and even death caused by SARS-CoV-2 variants, including Omicron.[24,36] It can be explained by the post-vaccination T-cell response in cross-recognizing the Omicron variant, contributing to adequate protection against severe disease.[37,38] Jingyou et al. recommended that booster vaccines would help our immunity system consistently produce an adequate level of neutralising antibodies against the Omicron variant of SARS-CoV-2.[39]

LIMITATIONS

There are some limitations to our study. First, the genomic sequencing data was not available to determine the predominance of COVID-19 sub-variance in our studied group; nevertheless, the variant predominance trends presumably occurred during the study period. Second, the follow-up duration was short. A longer period of observation is desirable to determine the outcome. Third,the methodology of our study was constructed based on the adaptation of previous guidelines on COVID-19 vaccination before a newer version was launched officially on April 1, 2022.

CONCLUSION

In this retrospective cohort study conducted during the period of Omicron prevalence, we concluded that COVID-19 severity may potentially rise with age and in the presence of comorbidities, as well as among unvaccinated individuals. In

light of the high transmissibility of the Omicron variant leading to a substantial surge of COVID-19 cases, the enormous volume of hospitalisation may heavily strain the local healthcare systems. The availability of local data can help in fine tuning the limited local healthcare resources during the Omicron onslaught. Furthermore, this data could assist in informing programme managers on admission criteria to avoid unnecessary admissions that burden hospitals; identifying high-risk individuals to target interventions, for instance, completing vaccinations and avoiding high-risk exposures; and prognosticating which patients will suitably benefit from timely treatment with antiviral or monoclonal antibodies.

ETHICS APPROVAL

For this study, we have obtained an approval from the National Medical Research Register, Ministry of Health, Malaysia.

CONFLICT OF INTERESTS

None to declare.

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