Table 2 (Continued)

	Canada (Ulloa et al., 2022)[31]		Bahrain (Kumar et al., 2022)[32]		Japan (Miyashita et al., 2022)[33]	
	N	Value (%)	N	Value (%)	N	Value (%)
Total Number of Patients	78,166	100.0	1,428	100.0	335	100.0
COVID-19 Strain(s)						
Omicron	41,216	52.7	*	*	*	*
Delta	36,950	47.3	636	44.5	*	*
Alpha	*	*	792	55.5	335	100.0
Sex						
Female	38,822	49.7	462	32.4	108	32.2
Omicron	20,562	26.3	*	*	*	*
Delta	18,260	23.4	137	9.6	*	*
Alpha	*	*	325	22.8	108	32.2
Male	39,234	50.2	866	60.6	227	67.8
Omicron	20,614	26.4	*	*	*	*
Delta	18,620	23.8	399	27.9	*	*
Alpha	*	*	467	32.7	227	67.8

Note. *=Data not reported

	Spain (Martínez-García et al., 2021)[34]		England (Twohig et al., 2022)[35]		Singapore (Ong et al., 2022)[36]	
	N	Value (%)	N	Value (%)	N	Value (%)
Total Number of Patients	426	100.0	43,338	100.00%	124	100.0
COVID-19 Strain(s)						
Omicron	*	*	*	*	*	*
Delta	*	*	8,682	20.0	67	54.0
Alpha	426	100.0	34,656	80.0	57	46.0
Sex						
Female	251	58.9	22,162	51.1	55	44.4
Omicron	*	*	*	*	*	*
Delta	*	*	4,249	9.8	33	26.6
Alpha	251	58.9	17,913	41.3	22	17.7
Male	175	41.1	21,176	48.9	69	55.6
Omicron	*	*	*	*	*	*
Delta	*	*	4,433	10.2	34	27.4
Alpha	175	41.1	16,743	38.6	35	28.2

Note. *=Data not reported

Kannan D, et al., Arch Clin Biomed Res 2023
DOI:10.26502/acbr.50170375

Table 2 (Continued)

		South Africa (Lin et al., 2022)[37]	
		N	Value (%)
Total Number of Patients		300	100.00%
COVID-19 Strain(s)			
	Omicron	300	100.00%
	Delta	*	*
	Alpha	*	*
Sex			
	Female	132	44.00%
	Omicron	132	44.00%
	Delta	*	*
	Alpha	*	*
	Male	168	56.00%
	Omicron	168	56.00%
	Delta	*	*
	Alpha	*	*

Note. *=Data not reported

	South Africa (Abdullah et al., 2022)[28]		China (Bi et al., 2022)[29]		Japan (Ito et al., 2022)[30]	
	N	Value (%)	N	Value (%)	N	Value (%)
Age						
60+	1,521	34.3	*	*	*	*
Omicron	1,521	34.3	*	*	*	*
Delta	*	*	*	*	*	*
Alpha	*	*	*	*	*	*
<60	2,877	65.0	*	*	*	*
Omicron	2,877	65.0	*	*	*	*
Delta	*	*	*	*	*	*
Alpha	*	*	*	*	*	*
Vaccination						
Zero Doses	*	*	*	*	80	34.6
Omicron	*	*	*	*	80	34.6
Delta	*	*	*	*	*	*
Alpha	*	*	*	*	*	*
1+ Doses	*	*	*	*	151	65.4
Omicron	*	*	*	*	151	65.4
Delta	*	*	*	*	*	*
Alpha	*	*	*	*	*	*

Note. *=Data not reported

Kannan D, et al., Arch Clin Biomed Res 2023
DOI:10.26502/acbr.50170375

Table 2 (Continued)

	Canada (Ulloa et al., 2022)[31]		Bahrain (Kumar et al., 2022)[32]		Japan (Miyashita et al., 2022)[33]	
	N	Value (%)	N	Value (%)	N	Value (%)
Age						
60+	*	*	*	*	198	59.1
Omicron	*	*	*	*	*	*
Delta	*	*	*	*	*	*
Alpha	*	*	*	*	198	59.1
<60	*	*	*	*	137	40.9
Omicron	*	*	*	*	*	*
Delta	*	*	*	*	*	*
Alpha	*	*	*	*	137	40.9
Vaccination						
Zero Doses	23,028	29.5	512	35.9	*	*
Omicron	7,634	9.8	293	20.5	*	*
Delta	15,394	19.7	219	15.3	*	*
Alpha	*	*	*	*	*	*
1+ Doses	55,138	70.5	916	64.1	*	*
Omicron	33,582	43.0	*	*	*	*
Delta	21,556	27.6	343	24.0	*	*
Alpha	*	*	573	40.1	*	*

Note. *=Data not reported

	Spain (Martínez-García et al., 2021)[34]		England (Twohig et al., 2022)[35]		Singapore (Ong et al., 2022)[36]	
	N	Value (%)	N	Value (%)	N	Value (%)
Age						
60+	*	*	2,718	6.3	*	*
Omicron	*	*	*	*	*	*
Delta	*	*	437	1.0	*	*
Alpha	*	*	2,281	5.3	*	*
<60	*	*	22,707	52.4	*	*
Omicron	*	*	*	*	*	*
Delta	*	*	8,245	19.0	*	*
Alpha	*	*	14,462	33.4	*	*
Vaccination						
Zero Doses	*	*	32,078	74.0	106	85.5
Omicron	*	*	*	*	*	*
Delta	*	*	6,255	14.4	49	39.5
Alpha	*	*	25,823	59.6	57	46.0
1+ Doses	*	*	11,260	26.0	18	14.5
Omicron	*	*	*	*	*	*
Delta	*	*	2,427	5.6	18	14.5
Alpha	*	*	8,833	20.4	0	0.0

Note. *=Data not reported

Table 2 (Continued)

		South Africa (Lin et al., 2022)[37]	
		N	Value (%)
Age			
	60+	*	*
	Omicron	*	*
	Delta	*	*
	Alpha	*	*
	<60	*	*
	Omicron	*	*
	Delta	*	*
	Alpha	*	*
Vaccination			
	Zero Doses	62	20.7
	Omicron	62	20.7
	Delta	*	*
	Alpha	*	*
	1+ Doses	238	79.3
	Omicron	238	79.3
	Delta	*	*
	Alpha	*	*

Note. *=Data not reported

	South Africa (Abdullah et al., 2022)[28]		China (Bi et al., 2022)[29]		Japan (Ito et al., 2022)[30]	
	N	Value (%)	N	Value (%)	N	Value (%)
Signs						
Fever	*	*	61	93.8	79	34.2
Omicron	*	*	61	93.8	79	34.2
Delta	*	*	*	*	*	*
Alpha	*	*	*	*	*	*
Pneumonia	*	*	*	*	*	*
Omicron	*	*	*	*	*	*
Delta	*	*	*	*	*	*
Alpha	*	*	*	*	*	*

Note. *=Data not reported

Table 2 (Continued)

	Canada (Ulloa et al., 2022)[31]		Bahrain (Kumar et al., 2022)[32]		Japan (Miyashita et al., 2022)[33]	
	N	Value (%)	N	Value (%)	N	Value (%)
Signs						
Fever	*	*	*	*	295	88.1
Omicron	*	*	*	*	*	*
Delta	*	*	*	*	*	*
Alpha	*	*	*	*	*	*
Pneumonia	*	*	*	*	*	*
Omicron	*	*	*	*	*	*
Delta	*	*	*	*	*	*
Alpha	*	*	*	*	*	*

Note. *=Data not reported

	Spain (Martínez-García et al., 2021)[34]		England (Twohig et al., 2022)[35]		Singapore (Ong et al., 2022)[36]	
	N	Value (%)	N	Value (%)	N	Value (%)
Signs						
Fever	*	*	*	*	81	65.3
Omicron	*	*	*	*	*	*
Delta	*	*	*	*	48	38.7
Alpha	*	*	*	*	33	26.6
Pneumonia	*	*	*	*	42	33.9
Omicron	*	*	*	*	*	*
Delta	*	*	*	*	33	26.6
Alpha	*	*	*	*	9	7.3

Note. *=Data not reported

	South Africa (Lin et al., 2022)[37]	
	N	Value (%)
Signs		
Fever	*	*
Omicron	*	*
Delta	*	*
Alpha	*	*
Pneumonia	*	*
Omicron	*	*
Delta	*	*
Alpha	*	*

Note. *=Data not reported

Kannan D, et al., Arch Clin Biomed Res 2023
DOI:10.26502/acbr.50170375

Table 3: Relative odds ratio and chi-squares association of contracting a certain COVID-19 strain based on potential risk factor (age, sex, and vaccination)

	South Africa (Abdullah et al., 2022)[28]		China (Bi et al., 2022)[29]		Japan (Ito et al., 2022)[30]	
	X^2 (P-Value)	OR (95% CI)	X^2 (P-Value)	OR (95% CI)	X^2 (P-Value)	OR (95% CI)
Sex	*	*	16.5 (0.00026)	*	58.3 (2.24E-13)	*
Age	1440 (<2.2E-16)	*	*	*	*	*
Vaccination	*	*	*	*	74.1 (<2.2E-16)	*

Note. [1] = Result is not significant (P-value > 0.05)

	Canada (Ulloa et al., 2022)[31]		Bahrain (Kumar et al., 2022)[32]		Japan (Miyashita et al., 2022)[33]	
	X^2 (P-Value)	OR (95% CI)	X^2 (P-Value)	OR (95% CI)	X^2 (P-Value)	OR (95% CI)
Sex	1.41 (0.495)[1]	0.98 (0.96–1.01)[1]	33.7 (4.70E-08)	0.49 (0.39–0.63)	115 (<2.2E-16)	*
Age	*	*	*	*	92.1 (<2.2E-16)	*
Vaccination	5020 (<2.2E-16)	3.14 (3.04–3.24)	52.0 (5.05E-12)	0.45 (0.36–0.56)	*	*

Note. [1] = Result is not significant (P-value > 0.05)

	Spain (Martínez-García et al., 2021)[34]		England (Twohig et al., 2022)[35]		Singapore (Ong et al., 2022)[36]	
	X^2 (P-Value)	OR (95% CI)	X^2 (P-Value)	OR (95% CI)	X^2 (P-Value)	OR (95% CI)
Sex	117 (<2.2E-16)	*	21.0 (2.79E-05)	0.90 (0.85–0.94)	1.42 (0.492)[1]	1.54 (0.75–1.65)[1]
Age	*	*	442 (<2.2E-16)	2.97 (2.68–3.10)	17.9 (1.29E-04)	*
Vaccination	*	*	22.0 (1.70E-05)	1.13 (1.08–1.20)	*	*

Note. [1] = Result is not significant (P-value > 0.05)

	South Africa (Lin et al., 2022)[37]	
	X^2 (P-Value)	OR (95% CI)
Sex	78.2 (<2.2E-16)	*
Age	*	*
Vaccination	152 (<2.2E-16)	*

Note. [1] = Result is not significant (P-value > 0.05)

Citation: Dharshini Kannan, Sreenidhi Muppiri, Maren Reid. Analysis of Potential Risk Factors of COVID-19 Based on Variants: Omicron, Delta, and Alpha. Archives of Clinical and Biomedical Research. 7 (2023): 590-603.

Kannan D, et al., Arch Clin Biomed Res 2023
DOI:10.26502/acbr.50170375

in an Alpha-Delta wave. Furthermore, the largest odds ratio was observed for vaccination and having Alpha in a Delta-Omicron wave

Discussion

COVID-19 strains have impacted regions across the world in various ways. It is necessary to understand the odds of contracting past COVID-19 strains to understand new COVID-19 strains better. This scenario facilitates the improved diagnosis of COVID-19 patients by identifying the specific strain they are infected with. Sex, age, and vaccination are the three characteristics of a COVID-19 patient that are well recorded, making it critical and reliable to understand the odds of contracting of COVID-19 strains based on these factors.

The latest studies on the association between getting infected by COVID-19 and certain demographics tend to focus on age, sex, and vaccination [9-12]. We observed a statistically significant association between age and contracting COVID-19 regardless of the strain in all the regions observed in the present study. The current study's findings align with previous research conducted in Europe, which has identified an association between age and contracting COVID-19 [4, 13]. The association between age and contracting COVID-19 (for any of the three strains in the present study) could depend on physiologic changes in the immune system such as immunosenescence due to aging [14, 15]. In the present study, a statistically significant association was identified between being vaccinated and getting infected with COVID-19, irrespective of the viral strain, in the regions studied. The findings of the present study are consistent with prior research, which has established a relationship between vaccine coverage and transmission of infection of COVID-19 variants across different regions globally [8, 16]. The observed association between vaccination and COVID-19 infection is likely explained by the vaccine's novel mechanism of action and overall immunology response, which is independent of geography [17-19]. Males tend to have a greater risk of COVID-19 infection than females [13, 20]. Although in this study, sex didn't always have a statistically significant association with the contracted COVID-19 strain, which aligns with the idea that males and females are at an equal risk of COVID-19 infection.21 The present study's findings wasn't a significant association of sex and testing positive for specific COVID-19 strains in Singapore and Canada, but the rest of the places included in the study had a significant association with sex and contracted COVID-19 strain. The present study's result can be interpreted as the nations that have sex equality in health don't have a significant association between sex and COVID-19 strains.

Prior research has established that males tend to have be at higher risk of COVID-19 infection than females [13, 20]. However, in the present study, the odds of contracting Delta among females are similar to the odds of males contracting Delta in a Delta-Omicron wave; nevertheless, males have lower odds of contracting Alpha than females in the Alpha-Delta wave. This is contradicting with the theory that female COVID-19 patients have higher levels of estrogen than male COVID-19 patients which may decrease the odds of severe infection of COVID-19 since estrogen has a role in the regulation of the immune response by interfering with B cell function, resulting in a Th2 response, while testosterone suppresses the natural killer cells' response [22, 23].

The administration of COVID-19 vaccinations serves as a crucial mechanism in minimizing the transmission and prevalence of the virus [8, 16, 24]. In the Alpha-Delta wave, vaccinated people have greater odds of getting Alpha in Bahrain, but unvaccinated people have slightly greater odds of contracting Alpha in England. In the Delta-Omicron wave, unvaccinated individuals have much higher odds of contracting Delta than the vaccinated individuals in Canada. These contradicting results can be best explained by countries like England and Canada having a plan to increase vaccination administration or knowledge of vaccine administration unlike countries like Bahrain in early 2021 [25-27]. Also, the vaccines used in Bahrain may not be approved - unlike the vaccines commonly used in England or Canada - so the vaccination in Bahrain may have not been as effective as those in Canada or England.

Aging has been known to decrease immunity since there are fewer immune cells in the body starting from around age 60 [4, 14]. In the present study, there is a higher odds of individuals 60 years and older contracting Alpha than individuals who are less than 60 years old in an Alpha-Delta wave. This can be attributed to the effect of fewer B and T cells that move from primary to secondary lymphoid organs in older individuals than in younger individuals [14, 23].

This study affirms that demographic factors such as sex and age and vaccination status have a significant association with COVID-19 strains depending on the location of the individual.

There are important limitations of the present meta-analysis. First, this study isn't a true meta-analysis; this study's purpose is to understand how COVID-19 is associated with factors such as sex, age, and vaccination. The next step would be to conduct a true meta-analysis once more studies are published on all COVID-19 strains. Second, bivariate associations don't account for confounding and effect modification when making public health inferences. For example, women may be more vulnerable to risk of COVID-19 infection than male in Canada because of factors such as pregnancy, or underlying diseases which weren't accounted for in this study. Future studies should model the

associations in a multivariate context to account for this. Finally, some sources have small sample sizes, preventing the data from being properly generalized to a larger population.

Despite studies being published with data on the demographics and vaccination of COVID-19 patients, there aren't many studies analyzing the data from sources based on different regions throughout the world. The findings from the present study provide meta-analytic estimates on the odds of getting infection by COVID-19 strain of interest based on demographic subgroups and vaccination. These results can inform the healthcare industry by identifying groups that are at risk of getting infected by certain COVID-19 strains and support the idea that the risk of infection by certain COVID-19 strains varies based on the location of the individual.

Acknowledgements

The authors thank Dr. Hamsa Subramaniam for her guidance and support as an advisor for this study.

Contributors

Concept and design: DK, MR

Acquisition, analysis, or interpretation of data: DK, SM

Drafting of the manuscript: DK

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: DK

All the authors contributed to the writing of the manuscript. All the authors agreed with the results and conclusions of the manuscript. All authors have read, and confirm that they meet, ICMJE criteria for authorship.

Potential Conflicts of Interest

All authors report no potential conflicts of interest.

Funding: None

References

1. Listings of WHO's response to COVID-19. World Health Organization (2021).
2. Kathy Katella. Omicron, Delta, Alpha, and More: What To Know About the Coronavirus Variants. Yale Medicine (2023).
3. Update on SARS CoV-2 Variant BA.2.86. Centers for Disease Control and Prevention (2023).
4. Sobotka T, Brzozowska Z, Muttarak R, et al. Age, gender and COVID-19 infections (2020).
5. Burn E, You SC, Sena A, et al. Deep phenotyping of 34,128 patients hospitalised with COVID-19 and a comparison with 81,596 influenza patients in America, Europe and Asia: an international network study (2020).
6. Kollamparambil U, Oyenubi A, Nwosu C. COVID19 vaccine intentions in South Africa: health communication strategy to address vaccine hesitancy. BMC Public Health 21 (2021).
7. Israel A, Merzon E, Schäffer AA, et al. Elapsed time since BNT162b2 vaccine and risk of SARS-CoV-2 infection: Test negative design study. The BMJ (2021): 375.
8. Vitiello A, Ferrara F, Troiano V, et al. COVID-19 vaccines and decreased transmission of SARS-CoV-2. Inflammopharmacology 29 (2021): 1357-1360.
9. Amelia Hill. Age, sex, vaccine dose, chronic illness – insight into risk factors for severe Covid is growing. The Guardian (2021).
10. Zhang J jin, Dong X, Liu G hui, et al. Risk and Protective Factors for COVID-19 Morbidity, Severity, and Mortality. Clin Rev Allergy Immunol 64 (2022): 90-107.
11. Vo AD, La J, Wu JTY, et al. Factors Associated With Severe COVID-19 Among Vaccinated Adults Treated in US Veterans Affairs Hospitals. JAMA Netw Open 5 (2022): 2240037.
12. Meister T, Pisarev H, Kolde R, et al. Clinical characteristics and risk factors for COVID-19 infection and disease severity: A nationwide observational study in Estonia 17 (2022): 0270192.
13. Shahbazi F, Solgi M, Khazaei S. Predisposing risk factors for COVID-19 infection: A case-control study. Caspian J Intern Med 11 (2020): 495-500.
14. Bajaj V, Gadi N, Spihlman AP, et al. Aging, Immunity, and COVID-19: How Age Influences the Host Immune Response to Coronavirus Infections? Front Physiol (2021): 11.
15. Stahl EC, Brown BN. Cell therapy strategies to combat immunosenescence. Organogenesis 11 (2015): 159-172.
16. Rahmani K, Shavaleh R, Forouhi M, et al. The effectiveness of COVID-19 vaccines in reducing the incidence, hospitalization, and mortality from COVID-19: A systematic review and meta-analysis 10 (203).
17. Zsuzsanna Jakab. Vaccines work at all ages, everywhere. World Health Organization (2020).
18. Pulendran B, Ahmed R. Immunological mechanisms of vaccination. Nat Immunol (2011): 509-517.
19. Rodrigues CMC, Plotkin SA. Impact of Vaccines; Health, Economic and Social Perspectives. Front Microbiol (2020): 11.

20. Ambrosino I, Barbagelata E, Ortona E, et al. Gender differences in patients with COVID-19: A narrative review. Monaldi Archives for Chest Disease 90 (2020): 318-324.

21. Mukherjee S, Pahan K. Is COVID-19 Gender-sensitive? J Neuroimmune Pharmacol 16 (2021): 38-47.

22. Taneja V. Sex hormones determines immune response. Front Immunol (2018): 9.

23. Ciarambino T, Para O, Giordano M. Immune system and COVID-19 by sex differences and age. Women's Health (2021): 17.

24. Huang C, Yang L, Pan J, et al. Correlation between vaccine coverage and the COVID-19 pandemic throughout the world: Based on real-world data. J Med Virol 94 (2022): 2181-2187.

25. Saleem F, Ahmed A, Faisal ES, et al. Knowledge and Practice of Immunization Among Primary Health Care Nurses in Bahrain. Journal of the Bahrain Medical Society 34 (2022): 19-26.

26. Zhang J, Yang H, Yang M, et al. The role of vaccines in COVID-19 control strategies in Singapore and China. Health Policy Technol 11 (2022): 100620.

27. Rachel Aiello. Canada plans to vaccinate everyone who wants it by the end of 2021. Bell Media (2020).

28. Abdullah F, Myers J, Basu D, et al. Decreased severity of disease during the first global omicron variant covid-19 outbreak in a large hospital in tshwane, south africa. Int J Infect Dis 116 (2022): 38-42.

29. Bi X, Zhang Y, Pan J, et al. Differences Between Omicron Infections and Fever Outpatients: Comparison of Clinical Manifestations and Initial Routine Hematology Indicators. Infect Drug Resist 15 (2022): 5111-5120.

30. Ito N, Kitahara Y, Miwata K, et al. Comparison of COVID-19 pneumonia during the SARS-CoV-2 Omicron wave and the previous non-Omicron wave in a single facility. Respir Investig 60 (2022): 772-778.

31. Ulloa AC, Buchan SA, Daneman N, et al. Early estimates of SARS-CoV-2 Omicron variant severity based on a matched cohort study, Ontario, Canada (2022).

32. Kumar N, Quadri S, AlAwadhi AI, et al. COVID-19 Recovery Patterns Across Alpha (B.1.1.7) and Delta (B.1.617.2) Variants of SARS-CoV-2. Front Immunol (2022): 13.

33. Miyashita N, Nakamori Y, Ogata M, et al. Clinical differentiation of severe acute respiratory syndrome coronavirus 2 pneumonia using the Japanese guidelines. Respirology 27 (2022): 90-92.

34. Martínez-García L, Espinel MA, Abreu M, et al. Emergence and spread of b.1.1.7 lineage in primary care and clinical impact in the morbi-mortality among hospitalized patients in madrid, spain. Microorganisms 9 (2021).

35. Twohig KA, Nyberg T, Zaidi A, et al. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. Lancet Infect Dis 22 (2022): 35-42.

36. Ong SWX, Chiew CJ, Ang LW, et al. Clinical and Virological Features of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Variants of Concern: A Retrospective Cohort Study Comparing B.1.1.7 (Alpha), B.1.351 (Beta), and B.1.617.2 (Delta). Clinical Infectious Diseases 75 (2022): 1128-1136.

37. Lin XQ, Lv L, Chen Y, et al. The impact of the Omicron epidemic on the health behavior in Cape Town, South Africa. One Health (2022): 14.