Exposure to SARS-CoV-2 in a high transmission setting increases the risk of severe COVID-19 compared to exposure to a low transmission setting?

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Highlight

Regardless of healthcare resource availability, the risk of severe COVID-19 outcomes is higher if infection occurs in a high transmission setting associated with repeat or constant exposure compared to a low transmission setting.

The Coronavirus Disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) initially emerged in Wuhan, Hubei province, China. By Feb 27, 2020, 48,137 cases and 2,132 deaths (mortality, 4.4%) were reported in Wuhan, whereas 13,045 cases and 109 deaths (mortality, 0.8%) were reported in other provinces of China (WHO situation report, 27 February 2020). The striking difference in mortality between Wuhan and other cities in China was partly attributed to insufficient medical services at the time when the health care system was overwhelmed in Wuhan.[1] However, the higher mortality persisted in Wuhan despite the fact that after the initial epidemic peak same clinical management guidelines were applied throughout China, and case fatality rates remained higher even when more medical personnel was deployed to Wuhan.

Wenzhou is located 900 kilometers east of Wuhan. A large number of Wenzhou citizens live and work in Wuhan and were hence infected during the early COVID-19 outbreak. Many of them returned from Wuhan to Wenzhou just before the lockdown of Wuhan[2], and Wenzhou had the highest incidence among all cities outside Hubei province. Of 1205 confirmed cases in Zhejiang province, 504 confirmed cases were reported in Wenzhou (504 cases, 5.6 cases/100,000) (WHO situation report 27 February 2020). The sudden lockdown of Wuhan provides a clear distinction between those persons who had been infected in Wuhan prior to return to Wenzhou and the secondary cases infected in Wenzhou due to contact to infected persons from Wuhan who had moved to Wenzhou. As all patients in Wenzhou received the same level of medical service, Wenzhou provides a unique opportunity to investigate the association between exposure to a high transmission intensity area (Wuhan) versus exposure to a low transmission area (Wenzhou) and the risk of severe COVID-19 outcomes. We set out to study risk factors for severe COVID-19 in those infected in Wuhan (coined "exposure to high transmission or high-epidemic area") versus those infected in Wenzhou (coined "non-exposure to high transmission area").

We retrospectively retrieved the epidemiological and clinical features of 192 patients with COVID-19. Seventy-six patients (76/192, 39.6%) had been infected in Wuhan (exposure group), and 116 (116/192, 62%) who were infected in Wenzhou (non-exposure). Both groups received the same standards of clinical management and care. The two groups were comparable according to gender distribution (50% versus 53% females in the exposure versus non-exposure group, respectively; p>0.99), age (45.4±12 and 46.3±15.4, *P*=0.67), days between the onset of COVID-19 and admission to hospital (6.2±3.3 and 6.3±3.9, *P*=0.86), and prevalence of underlying diseases that included hypertension, diabetes, and liver, pulmonary, renal,

cardiovascular diseases (30% and 33%, *P*=0.80). We defined the absence of a point source for the patients from Wuhan as follows: absence of a single close contact, history of having visited a hospital or a wet market, or history of staying in a confined space or residence where more than one infected person was reported within the preceding 14 days. A point source was defined as a known contact (SARS-CoV-2 positive person). We used a standard questionnaire form that included these criteria to determine the absence or presence of a point source.

Our results show that the exposure group had a significantly higher proportion of persons infected without a known source (63/76, 83% versus 6/116, 5%, *P*<0.0001) (Table 1). Only 13 of 76 (17%) patients in the exposure group had a point source determined compared to 110 of 116 (95%) patients in the non-exposure group. The exposure group had a higher incidence of severe COVID-19 outcomes compared to the non-exposure group (Table 1), as reflected by the following parameters, including higher temperature (37.4±0.8 versus 37.1±0.6 ℃, *P*=0.0034), lower white blood cell count (4.4±1.6 versus 5.2±1.7, $\times 10^9$/L, *P*=0.0013), lower lymphocyte count (1.07±0.52 versus 1.34±0.62, $\times 10^9$/L, *P*=0.002), higher creatine kinase (150±199 versus 103±107 U/L, *P*=0.035), and a higher proportion of severe and critically ill cases (30% [23/76] versus 9% [11/116], *P*<0.0001). The exposure group also had a slightly lower cycle threshold (Ct) values (28.5±5.6 versus 30.3±4.6, *P*=0.065) of RT-PCR for the ORF1 gene of SARS-CoV-2, which is inversely correlated with a slightly higher SARS-CoV-2 viral load. No significant difference was observed in any

of the other variables such as comorbidities, age, days between onset of symptoms and hospitalisation (P>0.05).

We then performed stepwise multivariate logistic regression (SPSS Statistics 22, IBM SPSS) and found that the Odds ratio (OR) for severe disease outcomes were "absence of a point source" (OR =6.3, *P*=0.0015), decreased lymphocyte count (OR=17.4, *P*<0.0001), and elevated CRP (OR=40, *P*<0.0001) (Table 1).

Discussion:

We found a high Odds Ratio for severe COVID-19 outcomes for those who had been infected in the high transmission setting of Wuhan, especially if no point source was identified, compared to those infected in a low transmission setting. While decreased lymphocyte count and elevated CRP are known risk factors predictive of severe disease[3], we believe this is the first study that showed exposure to a high transmission setting increases the risk for disease severity. We hypothesize that this is due to repeat exposure to multiple points of transmission sources or contacts in a setting with wide community transmission such as Wuhan early on in the outbreak. We found that the viral load in patients infected in the high transmission setting of Wuhan was higher than for those infected in the low transmission setting of Wenzhou. A viral dose-dependent immune response may be associated with more disease severity and hence the higher mortality observed in Wuhan, as previously reported.[4] Indeed, the exposure group had a higher viral load, higher temperature and lower lymphocyte

count compared to the non-exposure group indicating enhanced immune responses and exhaustion of immune cells due to persistent and large-scaled viral infection.[5] Similarly, in the epicentre in Northern Italy, a very high case fatality rate was reported during the height of the outbreak.[6] The high mortality in Northern Italy was also initially attributed to the fact that hospitals were overwhelmed by the onstorm of cases. But maybe there is another factor inherent to high transmission settings that lead to a higher case fatality rate as observed in our study? In our study, we were able to exclude any differences in healthcare systems and clinical management as a confounding factor for severity.

In conclusion, our study highlights that SARS-CoV-2 infection in a hotspot or epicentre with high transmission intensity may adversely impact mortality rates compared to infection in a low transmission area. We hypothesize that repeat or constant exposure to the widely circulating virus could explain this phenomenon. However, our study was only an observational study, and can only provide indirect ecological evidence. More studies in other settings and countries are necessary to elucidate to what extent repeat exposure may increase the risk of more severe COVID-19 disease outcomes and relevant immunological mechanisms.

Ethics approval and consent to participate

This study was approved by The Ding Li Clinical College of Wenzhou Medical University and Sixth People's Hospital of Wenzhou. Oral consent was acquired from all patients.

Authors' contributions

*These authors contributed equally to the article. All authors read and approved the final manuscript.

Competing interests

All authors declare no conflict of interests.

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Table 1. Comparison and multivariate analysis of epidemiological and clinical features between the group exposed to a high-epidemic area and the group exposed to a low-endemic area

		Comparison between two groups		
Attribute (reference values)	Total	Exposure	Non-exposure	*P*
No. of patients	192	76	116	–
Female	100 (52%)	38 (50%)	62 (53%)	>0.99
Age (year)	46.0±14.1	45.4±12.0	46.3±15.4	0.67
	[43.2–48.5]	[42.5–48]	[43.5–49]	
Underlying disease	61 (32%)	23 (30%)	38 (33%)	0.8
Cough	123 (64%)	53 (70%)	70 (60%)	0.20
Sore throat	13 (7%)	6 (8%)	7 (6%)	0.80
Vomiting	10 (5%)	4 (5%)	6 (5%)	>0.99
Diarrhea	76 (39%)	34 (45%)	42 (36%)	0.30
Pulmonary infection	182 (95%)	72 (95%)	110 (95%)	>0.99

Days between onset and admission	6.3±3.6 [5.1–7.3]	6.2±3.3 [5.0–7.1]	6.3±3.9 [4.9–7.3]	0.86
Temperature (℃)	37.2±0.7 [37.0–37.4]	37.4±0.8 [37.2–37.5]	37.1±0.6 [36.9–37.3]	0.0034
Ct_ORF1	29.5±5.1 [28.6–30.5]	28.5±5.6 [27–30.1]	30.3±4.6 [29.2–31.4]	0.065
Lactate dehydrogenase (90–240 U/L)	212±67 [204–227]	227±87 [197–246]	220±76 [200–235]	0.56
Alanine amino transferase (<40 U/L)	29±27 [26–34]	30±21 [23–36]	29±20 [24–34]	0.74
Aspartate amino transferase (<40U/L)	30±19 [27–33]	32±21 [26–36]	29±19 [25–32]	0.31
Creatinine (30–110 umol/L)	69±34 [64–129]	69±33 [65–73]	64±30 [61–70]	0.28
Blood urea nitrogen (3–7 mmol/L)	3.8±1.1 [3.7–4.2]	3.8±1.0 [3.6–4]	3.7±1.2 [3.6–4.1]	0.55
Oxygen partial pressure (10.6–13.3 kPa)	12.7±4.1 [12.4–13.8]	12.2±3.1 [12–13.4]	13±4.7 [12.6–14]	0.19
Severe and critically ill cases	34 (19%)	23 (30%)	11 (9%)	<0.0001
Independent variables (x)				
C-reactive protein (<8 mg/L)	21±23 [16–23]	21±24 [16–27]	20±22 [16–26]	0.77
Temperature (℃)	37.2±0.7	37.4±0.8	37.1±0.6	0.0034

	[37.0–37.4]	[37.2–37.5]	[36.9–37.3]	
No point source contact established	69 (36%)	63 (83%)	6 (5%)	<0.0001
White blood cell (4–10 ×10^9/L)	5.0±1.8	4.4±1.6	5.2±1.7	0.0013
	[4.7–5.3]	[4–4.7]	[4.8–5.7]	
Lymphocyte (1.1–3.2 ×10^9/L)	1.23±0.60	1.07±0.52	1.34±0.62	0.0020
	[1.17–1.36]	[0.94–1.17]	[1.24–1.46]	
Creatine kinase (40–170 U/L)	122±167	150±199	103±107	0.035
	[93–162]	[67–230]	[84–121]	

Multivariate Analysis

Assignment	OR (95% CI)	*P*
0, normal; 1, elevated	40.0 (9.0–300)	<0.0001
0, normal; 1, elevated	1.8 (0.6 – 5.6)	0.31
0, point exposure; 1, repeat exposure	6.3 (2.1–20.9)	0.0015
0, normal; 1, decreased	0.7 (0.2–1.9)	0.45
0, normal; 1, decreased	17.4 (4.6–60.4)	<0.0001
0, normal; 1, elevated	1.0 (0.3–3.5)	0.96

Abbreviations: SD, standard deviation; Ct, threshold cycle; CI, confidence interval.

Note: Continuous variables are described as mean±SD [95% CI]. The categorical variables are described as counts and percentages (%).