

A Significance of High Prevalence of Diabetes and Hypertension in Severe COVID-19 Patients

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To the Editor

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19) has reached a pandemic level. In a recent retrospective cohort study of COVID-19, comorbidities such as diabetes and hypertension were present in nearly half of patients [1]. The odds of in-hospital death were significantly higher in patients with diabetes (2.85) and hypertension (3.05) [1].

It remains unknown why the prevalence of diabetes and hypertension is high in COVID-19 patients and why such diseases can be risk for severe COVID-19 including death.

To elucidate such clinical questions, I searched the prevalence of diabetes and hypertension and the controlling status of such diseases in all COVID-19 patients, severe and non-severe COVID-19 patients using PubMed. The prevalence of each disease in severe and non-severe COVID-19 patients was meta-analyzed by Peto's exact method, and odds ratio (OR) with 95% confidence interval (CI) was shown.

The prevalence of diabetes in all COVID-19 patients, severe and non-severe COVID-19 patients were shown in Table 1 [1-12]. Half of studies showed a statistically significantly higher prevalence of diabetes in severe patients than in non-severe patients. In the meta-analysis, the prevalence of diabetes in severe patients was significantly higher than that in non-severe patients (OR: 3.52, 95% CI: 2.65 - 4.67). Unfortunately, only three studies were available to analyze the controlling status of diabetes. All three studies showed that plasma glucose levels in severe patients were significantly higher than those in non-severe patients. Although such data did not present sufficient evidence, elevation of plasma glucose is likely to be associated with severity of COVID-19. Zhu et al performed a retrospective, multi-centered study of 7,337 cases of COVID-19 in Hubei Province, China, among which 952 had pre-existing type 2 diabetes [13]. They found that subjects with type 2 diabetes required more medical interventions, and had a significantly higher mortality (7.8% vs. 2.7%) and multiple organ injury than the non-diabetic

individuals. Further, well-controlled blood glucose was associated with markedly lower mortality compared to individuals with poorly controlled blood glucose, supporting a significance of hyperglycemia in severe COVID-19.

The prevalence of hypertension in all COVID-19 patients, severe and non-severe COVID-19 patients was shown in Table 2 [1-12]. Five of 12 studies showed a statistically significantly higher prevalence of hypertension in severe patients than in non-severe patients. In the meta-analysis, the prevalence of hypertension in severe patients was significantly higher than that in non-severe patients (OR: 2.69, 95% CI: 2.16 - 3.34). Seven studies were available to analyze the controlling status of hypertension. Five studies did not show any difference in blood pressure between severe and non-severe patients. Huang et al showed that systolic blood pressure was significantly higher in severe patients than in non-severe patients [2]. Itelman et al showed that minimal systolic blood pressure was significantly lower in severe patients than in non-severe patients, and maximal systolic blood pressure was significantly higher in severe patients than in non-severe patients [11]. Blood pressure itself is unlikely to be associated with severity of COVID-19. Since hypertension is one of the most significant risk factors for severe disease and mortality in COVID-19, and angiotensin-converting enzyme (ACE) 2 is the entry receptor of SARS-CoV-2 [14, 15], the effects of ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in COVID-19 patients have received much focus. A recent study has shown the protective effects of ACEIs/ARBs against mortality in COVID-19 [16], challenging the association between ACEIs/ARBs use and severe COVID-19.

Why is hypertension one of the most significant risk factors for severe disease and mortality in COVID-19? Diabetes and hypertension are crucial coronary risk factors, and diabetes and hypertension are closely interlinked because of similar risk factors, such as endothelial dysfunction, vascular inflammation, arterial re-modelling, atherosclerosis, dyslipidemia, and obesity [17]. Common mechanisms, such as upregulation of the renin-angiotensin-aldosterone system, oxidative stress, inflammation, and activation of the immune system likely contribute to the close relationship between diabetes and hypertension [17]. High prevalence of diabetes and hypertension in severe COVID-19 patients can be explained by such vascular damage. The prevalence of cardiovascular disease (CVD) in all COVID-19 patients, severe and non-severe COVID-19 patients was shown in Table 3 [1-8, 10-12]. Four of 11 studies showed a statistically significantly higher prevalence of CVD in severe patients than in non-severe patients. In the meta-analysis, the prevalence of

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Table 1. Prevalence of Diabetes in COVID-19 Patients

	All patients	Severe patients	Non-severe patients	P value
Huang et al, 2020 [2]	8/41 (20%)	1/13 (8%)	7/28 (25%)	0.16
Zhang et al, 2020 [3]	17/140 (12.1%)	8/58 (13.8%)	9/82 (11%)	0.615
Wang et al, 2020 [4]	14/138 (10.1%)	8/36 (22.2%)	6/102 (5.9%)	0.009
Wu et al, 2020 [5]	22/201 (10.9%)	16/84 (19%)	6/117 (5.1%)	0.002
Zhou et al, 2020 [1]	36/191 (19%)	17/54 (31%)	19/137 (14%)	0.0051
Wan et al, 2020 [6]	12/135 (8.9%)	9/40 (22.5%)	3/95 (3.1%)	NA
Guan et al, 2020 [7]	30/1,590 (8.2%)	19/130 (14.6%)	80/1,460 (5.5%)	NA
Wang et al, 2020 [8]	54/339 (16%)	11/65 (17.2%)	43/274 (15.8%)	0.116
Chen et al, 2020 [9]	14/145 (9.7%)	7/43 (16.3%)	7/102 (6.9%)	0.08
Hu et al, 2020 [10]	47/323 (14.6%)	11/26 (42.3%)	14/151 (9.3%)	< 0.001
Itelman et al, 2020 [11]	30/162 (18.5%)	11/92 (30.8%)	8/26 (12%)	0.04
Huang et al, 2020 [12]	19/202 (9.4%)	8/23 (34.8%)	11/179 (6.1%)	< 0.001

P values indicate a statistically significant difference between severe and non-severe patients. NA: not available; COVID-19: coronavirus disease 2019.

CVD in severe patients was significantly higher than that in non-severe patients (OR: 5.37, 95% CI: 3.73 - 7.74). Further, CVD was significantly associated with increased odds of death (OR: 21.4) [1], supporting a significant association between vascular damage and severity of COVID-19.

D-dimer is detected in injured vascular endothelium [18], and von Willebrand factor is produced by endothelial cells in response to injury, and high von Willebrand factor level has been observed in systemic vasculitis [19]. Multivariable regression showed increasing odds of in-hospital death associated with D-dimer greater than 1 µg/mL (OR: 18.42, 95% CI: 2.64 - 128.55; P = 0.0033) on admission [1]. Elevated von Willebrand factor levels were observed in COVID-19 patients in the intensive care unit [20]. D-dimer was also reported to be significantly increased in Kawasaki disease with coronary artery lesions, and to

be the independent risk for coronary artery lesions in Kawasaki disease [21]. Von Willebrand factor parameters were reported to represent potential biomarkers for disease activity and coronary artery lesion in patients with Kawasaki disease [22]. A very recent article reported the development of Kawasaki disease in COVID-19 patient [23], supporting an association between endothelial injury and severe COVID-19.

In conclusion, endothelial injury may be associated with severity of COVID-19, which can partially explain high prevalence of diabetes and hypertension in severe COVID-19.

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Table 2. Prevalence of Hypertension in COVID-19 Patients

	All patients	Severe patients	Non-severe patients	P value
Huang et al, 2020 [2]	6/41 (15%)	2/13 (15%)	4/28 (14%)	0.93
Zhang et al, 2020 [3]	42/140 (30%)	22/58 (37.9%)	20/82 (24.4%)	0.085
Wang et al, 2020 [4]	43/138 (31.2%)	21/36 (58.3%)	22/102 (21.6%)	< 0.001
Wu et al, 2020 [5]	39/201 (19.4%)	23/84 (27.4%)	16/117 (13.7%)	0.02
Zhou et al, 2020 [1]	58/191 (30%)	26/54 (48%)	32/137 (23%)	0.0008
Wan et al, 2020 [6]	13/135 (9.6%)	4/40 (10%)	9/95 (9.4%)	NA
Guan et al, 2020 [7]	269/1,590 (16.9%)	38/269 (14.1%)	61/1,321 (4.6%)	NA
Wang et al, 2020 [8]	138/339 (40.8%)	32/65 (50%)	106/274 (38.8%)	0.031
Chen et al, 2020 [9]	22/145 (15.2%)	9/43 (20.9%)	13/102 (12.7%)	0.21
Hu et al, 2020 [10]	105/323 (32.5%)	10/26 (38.5%)	39/151 (25.8%)	0.056
Itelman et al, 2020 [11]	49/162 (30.2%)	13/26 (50%)	18/92 (19.6%)	0.002
Huang et al, 2020 [12]	29/202 (14.4%)	2/23 (8.7%)	27/179 (15.1%)	0.411

P values indicate a statistically significant difference between severe and non-severe patients. NA: not available; COVID-19: coronavirus disease 2019.

Table 3. Prevalence of Cardiovascular Disease in COVID-19 Patients

	All patients	Severe patients	Non-severe patients	P value
Huang et al, 2020 [2]	6/41 (15%)	3/13 (23%)	3/28 (11%)	0.32
Zhang et al, 2020 [3]	7/140 (5%)	4/58 (6.9%)	3/82 (3.7%)	0.448
Wang et al, 2020 [4]	20/138 (14.5%)	9/36 (25%)	11/102 (10.8%)	0.04
Wu et al, 2020 [5]	8/201 (4%)	5/84 (6%)	3/117 (2.6%)	0.4
Zhou et al, 2020 [1]	15/191 (8%)	13/54 (24%)	2/137 (1%)	< 0.0001
Wan et al, 2020 [6]	7/135 (5.2%)	6/40 (15%)	1/95 (1%)	NA
Guan et al, 2020 [7]	59/1,590 (3.7%)	8/59 (13.6%)	91/1,531 (5.9%)	NA
Wang et al, 2020 [8]	53/339 (14.2%)	21/65 (32.8%)	32/274 (11.7%)	< 0.001
Hu et al, 2020 [10]	41/323 (12.7%)	11/26 (42.3%)	8/151 (5.3%)	< 0.001
Itelman et al, 2020 [11]	12/162 (7.4%)	4/26 (15.4%)	5/92 (5.4%)	0.228
Huang et al, 2020 [12]	5/202 (2.5%)	1/23 (4.3%)	4/179 (2.2%)	0.539

P values indicate a statistically significant difference between severe and non-severe patients. NA: not available; COVID-19: coronavirus disease 2019.

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Conflict of Interest

The author declares that he has no conflict of interest concerning this article.

Informed Consent

Not applicable.

Author Contributions

HY designed the research, collected and analyzed data, and wrote and approved the final paper.

Data Availability

The author declares that data supporting the findings of this study are available within the article.

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