Impact of COVID-19 on motility practices: new onset gastrointestinal and autonomic dysfunction after COVID-19 and the effects of vaccination in a nationwide cohort study

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Background

COVID-19 has been linked to a higher risk of enteric and autonomic dysfunction, but studies have been limited by small sample sizes and follow-up.

Methods

We performed a retrospective cohort study using the TriNetX Research Network, including over 80M patients from 57 academic medical centers in the US. Using ICD-10 and CPT codes, patients diagnosed with COVID-19 between Jan 1 to Dec 31, 2020 were propensity score matched for risk factors to:

- Negative controls (NC)
- Influenza
- Lyme's disease (LD)
- Infectious Mononucleosis (IM)
- Herpes Zoster (HZ)
- Varicella Zoster (VZ)
- Cytomegalovirus (CMV)

A Kaplan-Meier analysis was used to estimate the hazard ratio (HR) and cumulative incidence (CI) of new-onset outcomes within 3 months and 1 year after the diagnosis of the respective health event, including:

- GI symptoms or diagnoses
- Autonomic neuropathy (AN)
- Sensory neuropathy (SN)
- Motor neuropathy (MN).

We quantified the impact of prior vaccination for COVID-19 on these outcomes.

Results

A total of 1,355,657 COVID-19 patients were matched to 1,889,175 NCs, 698,253 Influenza, 61,826 IM, 129,246 LD, 457,984 HZ, 45,811 VZ, and 8,441 CMV patients.

- Both the risk of GI diagnoses and AN were increased (HR>1, p<0.05) after COVID-19 compared to every other control population, except for GI diagnoses after CMV (HR 0.89, p:0.26).
- COVID-19 significantly (p<0.05) increased the risk of vomiting (HR 1.78), nausea (HR 1.54) and irritable bowel syndrome (HR 1.07) compared to NCs, but it did not differ with that observed after Influenza (p>0.05).
- Although COVID-19 increased the risk of developing functional dyspepsia (HR 1.09), inflammatory bowel disease (HR 1.5) and abdominal pain (HR 1.38) compared to NCs, a diagnosis of Influenza yielded an even higher risk (p<0.05); for all other GI diagnoses, the risk was increased (p<0.05) compared to both NCs and Influenza.

Prior vaccination did not alter the risk of developing GI outcomes after COVID-19 (HR 0.95; p:0.32), but it did increase the risk of AN (HR 1.13, p:0.02) and MN (HR 1.6, p<0.05).

Table 1: Kaplan Meier analysis comparing new-onset outcomes between patients diagnosed with COVID-19 and a matched Influenza and negative control cohort. Outcomes are presented as a HR, in which the numerator consists of the COVID-19 population. The cumulative incidence of the outcomes between 3 months and 1 year after the index is presented for each cohort. A P-value was calculated using a log-rank test.

	COVID-19 vs Negative controls (n=1,889,175)				COVID-19 vs Influenza (n=698,253)			
New-onset outcomes	**HR (95% CI)**	**Probability COVID**	**Probability NC**	**P-value**	**HR (95% CI)**	**Probability COVID**	**Probability Influenza**	**P-value**
Gastrointestinal (GI) symptoms or diagnoses	1.37 (1.35 - 1.39)	11.43%	8.44%	<0.001	1.04 (1.03 - 1.06)	11.41%	10.87%	<0.001
Dysphagia	1.37 (1.33 - 1.41)	1.4%	1.03%	<0.001	1.18 (1.14 - 1.23)	1.23%	1.03%	<0.001
Gastro-esophageal reflux disease	1.30 (1.28 - 1.33)	4.21%	3.23%	<0.001	1.13 (1.11 - 1.16)	3.97%	3.5%	<0.001
Heartburn	1.15 (1.09 - 1.21)	0.42%	0.37%	<0.001	1.20 (1.12 - 1.28)	0.44%	0.36%	<0.001
Nausea	1.54 (1.50 - 1.58)	2.39%	1.56%	<0.001	1.12 (1.09 - 1.15)	2.51%	2.24%	<0.001
Vomiting	1.78 (1.71 - 1.85)	0.87%	0.49%	<0.001	1.04 (0.99 - 1.08)	0.9%	0.87%	0.116
Early satiety	1.31 (1.20 - 1.43)	0.15%	0.12%	<0.001	1.63 (1.44 - 1.85)	0.14%	0.09%	<0.001
Abdominal and pelvic pain	1.38 (1.36 - 1.41)	6.38%	4.63%	<0.001	0.97 (0.96 - 0.99)	6.62%	6.74%	0.01
Bloating	1.28 (1.24 - 1.33)	1.01%	0.78%	<0.001	1.29 (1.24 - 1.35)	0.97%	0.75%	<0.001
Gastroparesis	1.47 (1.35 - 1.60)	0.18%	0.12%	<0.001	1.39 (1.25 - 1.55)	0.17%	0.12%	<0.001
Functional dyspepsia	1.09 (1.02 - 1.17)	0.22%	0.2%	0.016	0.79 (0.73 - 0.86)	0.21%	0.27%	<0.001
Constipation	1.35 (1.32 - 1.38)	2.61%	1.94%	<0.001	1.17 (1.14 - 1.21)	2.4%	2.04%	<0.001
Diarrhea	1.53 (1.49 - 1.57)	2.62%	1.71%	<0.001	1.01 (0.98 - 1.03)	2.63%	2.61%	0.631
Irritable bowel syndrome	1.07 (1.02 - 1.12)	0.5%	0.47%	0.006	1.04 (0.98 - 1.10)	0.52%	0.5%	0.188
Inflammatory bowel disease	1.50 (1.45 - 1.56)	1.06%	0.71%	<0.001	0.75 (0.72 - 0.78)	1.05%	1.4%	<0.001
Autonomic neuropathy	1.32 (1.30 - 1.34)	8.69%	6.64%	<0.001	1.15 (1.13 - 1.17)	8.22%	7.1%	<0.001
Postural symptoms	1.43 (1.41 - 1.46)	5.89%	4.15%	<0.001	1.15 (1.13 - 1.18)	5.64%	4.88%	<0.001
Urinary dysfunction	1.22 (1.19 - 1.25)	2.76%	2.26%	<0.001	1.12 (1.09 - 1.16)	2.53%	2.24%	<0.001
Sexual dysfunction	0.99 (0.95 - 1.03)	0.66%	0.66%	0.751	1.04 (0.98 - 1.10)	0.59%	0.56%	0.168
Exocrine gland dysfunction	1.22 (1.18 - 1.26)	1.24%	1.02%	<0.001	1.26 (1.21 - 1.31)	1.17%	0.93%	<0.001
Sensory neuropathy	1.12 (1.09 - 1.15)	1.71%	1.53%	<0.001	0.89 (0.86 - 0.92)	1.69%	1.89%	<0.001
Motor neuropathy	1.22 (1.19 - 1.25)	1.52%	1.25%	<0.001	0.98 (0.95 - 1.01)	1.47%	1.49%	0.247

Conclusion

This nationwide analysis reveals that COVID-19 increases the risk of new-onset ENS and ANS dysfunction compared to NCs and patients infected by neurotrophic and non-neurotrophic pathogens, but less pronounced compared to CMV. Given the magnitude of COVID-19 infections, a significant increase in patients with dysmotility and ANS dysfunction is expected, for which Gastroenterology as a specialty needs to prepare.

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