COVID-19 Male Patients with Gastrointestinal Symptoms are at Higher Risk of Poor Clinical Outcomes but Not Mortality in Low Prevalence Areas

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Abstract

COVID-19 has been reported to cause gastrointestinal (GI) manifestations. However, there is limited data regarding the association between GI symptoms and clinical outcomes including mortality in low population density. Using TriNetX, a real-time analysis was performed for patients diagnosed with COVID-19 at Penn State Milton S. Hershey Medical Center. Our study, including a cohort of male and female patients (220), showed that the COVID-19 male patients with GI symptoms have higher risk for respiratory failure and hospitalization, but not mortality, compared to male patients without GI symptoms or female patients (with or without GI symptoms). Our study provides unique perspective of the impact of COVID-19-related mortality in low-density areas independent of GI symptoms.

Keywords: COVID-19; Gastrointestinal Symptoms; Respiratory Failure; Mortality

Introduction

Coronavirus infection (COVID-19), caused by SARS-CoV-2, was declared a global pandemic in early 2020. Although primarily a respiratory illness, gastrointestinal intestinal symptoms also appear to play a prominent role in disease pathogenesis [1-3]. COVID-19 causes a wide range of clinical symptoms, ranging from mild to critical illness, hospitalizations, death by sepsis and acute respiratory distress syndrome (ARDS) [4]. Clinical features of multiple organ failure occur sequentially or together, suggesting that they result from a final common pathway [5,6]. Our aim in this study was to determine the association between GI symptoms and several clinical outcomes in a cohort of COVID-19 patients at Penn State Milton S. Hershey Medical Center, an academic teaching hospital in the United States located in Dauphin County PA, a region with low local prevalence of COVID-19 infection.

Methods

Using TriNetX (Cambridge, MA, USA), a real-time search and analysis was performed for 220 patients (≥18 year's age) diagnosed with COVID-19 at Penn State Health. TriNetX (Cambridge, MA, USA), is a global federated health research network providing access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information). The TriNetX platform uses

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aggregated counts and statistical summaries of de-identified patient information. No protected health information (PHI) or personal data is made available to the users of the platform. TriNetX de-identifies and protects patient counts to safeguard protected health information by rounding patient counts in analyses up to the nearest 10.

Patients were stratified into two groups based upon the presence or absence of GI symptoms (diarrhea, infectious gastroenteritis and colitis, vomiting and nausea). Outcomes studied were respiratory failure, hospitalization and mortality, occurring within the 2 weeks after COVID-19 diagnosis.

Description of the Data Source

TriNetX (Cambridge, MA, USA) Penn State HCO Network incorporates COVID-19 specific diagnosis and terminology following the World Health Organization (WHO) and Centers for Disease Control (CDC) COVID-19 criteria. TriNetX uses de-identified clinical data along with the analytics to analyze research questions and aggregates them directly from the electronic medical records of the participating HCO.

Selection of COVID-19 Patients

TriNetX identified potential COVID-19 patients on or after January 20th through May 17th 2020, as per the CDC COVID-19 coding guidelines. These codes included Clinical Modification (ICD-10-CM) codes U07.1 (COVID-19, virus identified), U07.2 (COVID-19, virus not identified 9 WHO), B34.2 (Coronavirus infection, unspecified), B97.29 (Other coronavirus as the cause of diseases classified elsewhere) and J12.81 (Pneumonia due to SARS-2 associated coronavirus). Patients identified with diagnosis code 079.89 (Other specified viral infection) were excluded.

Selection of Patients with GI Symptoms Associated with Clinical Outcomes

Queries for patients who presented with GI symptoms were made using the ICD-10-CM codes R11.0 (nausea), R11.1 (vomiting), R11.2 (nausea and vomiting, unspecified), R19.7 (diarrhea, unspecified), K59.1 (functional diarrheas) and A09 (infectious gastroenteritis and colitis).

Study Outcomes

The time window to estimate all outcomes was up to 14 days from the day of COVID-19 diagnosis. The outcomes examined were the risk of respiratory failure, hospitalization and mortality. Respiratory failure was defined by the following ICD 10 codes: J80 (acute respiratory distress syndrome), J96.0 (a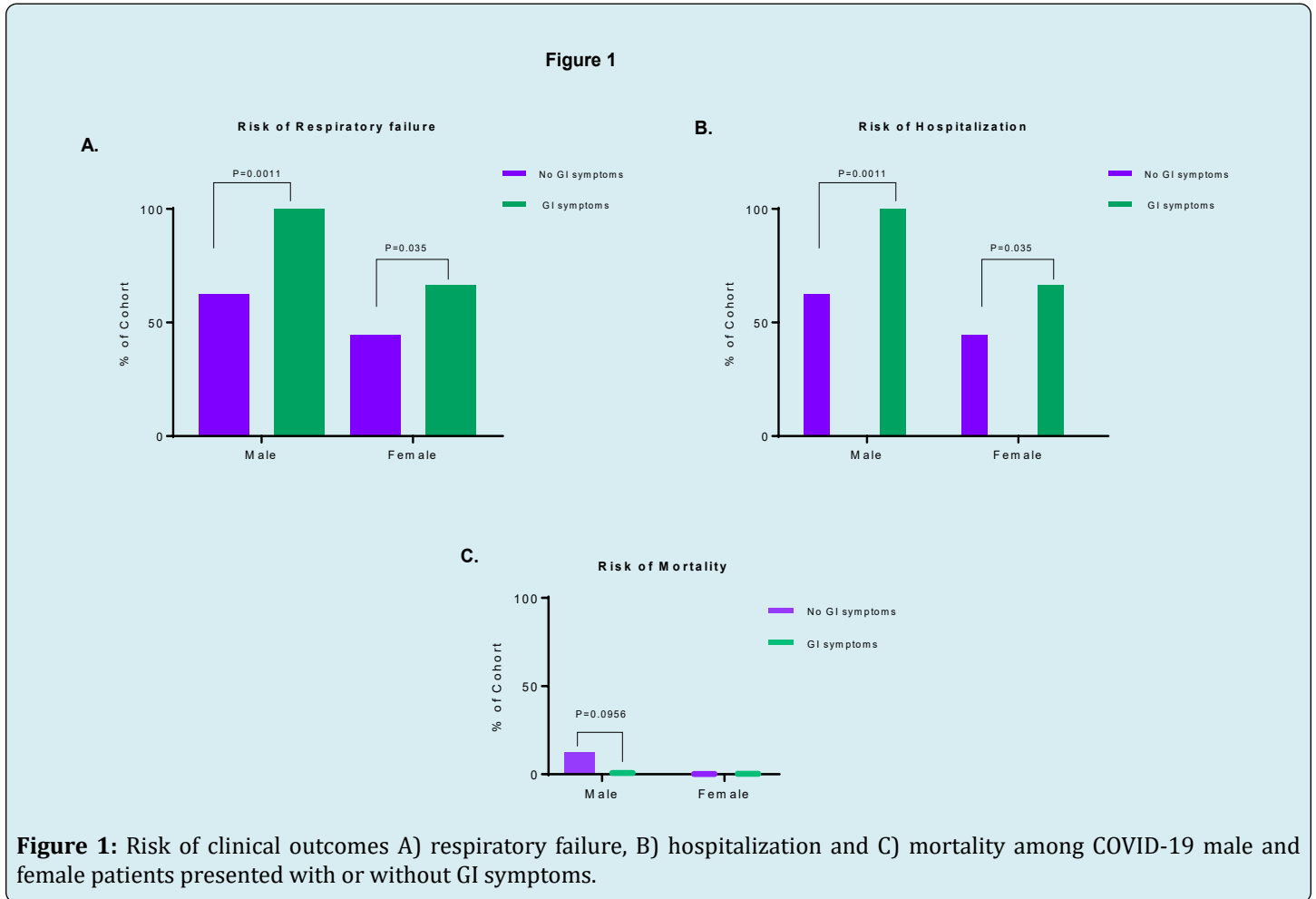cute respiratory failure), J96.1 (chronic respiratory failure), J96.2 (acute and chronic respiratory failure), J18.9 (pneumonia unspecified organism), R06.03 (acute respiratory distress), R06.00 (dyspnea, unspecified), and R06.02 (shortness of breath). Hospitalization was categorized by visit type within TriNetX and included CPT codes 1013659 (hospital inpatient services), 1013729 (clinical care services) and 1013699 (initial inpatient consultation services).

Statistical Analysis

All statistical analyses were performed in real-time using TriNetX. The means and standard deviations were used to describe and compare patient characteristics. Measures of association were computed to determine the risk of experiencing each outcome between the two study cohorts (presence or absence of GI symptoms). The risk difference computed the difference in risk between cohorts (Risk Ratio = Risk for Cohort 1 / Risk for Cohort 2, +/- 95% CI). Kaplan Meier analysis was performed to assess the probability of each study cohort surviving each study outcome.

Results

Association analysis was performed to assess differences in outcome between COVID-19 patients with and without GI symptoms. Data from 220 COVID-19 patients (ages 18 and older) (100 males and 120 females) was evaluated (Table 1). 22.7% (50) of cases exhibited GI symptoms (20 males and 30 females), including diarrhea, vomiting and nausea within the 2 weeks before or after COVID-19 diagnosis. Respiratory failure was present in 60% of patients with GI symptoms compared to 52.9% of patients with no GI symptoms (RR 0.882, 95% CI 0.676-1.152, p-value 0.378). A need for hospitalization was present in 60% of patients with GI symptoms compared to 47% of patients without GI symptoms (RR 0.784, 95% CI 0.595-1.034, p-value 0.107). Subgroup analysis based upon gender in each patient cohort (GI vs. no GI symptoms) demonstrated gender-based outcomes differences (Table 2). GI symptoms were more prevalent among female patients (25% vs. 20%). The presence of respiratory failure and need for hospitalization was present in 100% of males with GI symptoms vs. 62.5% without GI symptoms (RR 0.625, 95% CI 0.527-0.741, p-value 0.0011) and in 66.6% of females with GI symptoms vs. 44% without GI symptoms (RR 0.667, 95% CI 0.473-0.939, p-value 0.0350) (Figure 1A & B). Interestingly, mortality risk was greater among males without GI symptoms, 12.5% vs. 0% in males and females respectively (Figure 1C). This finding may be due to the larger number of older male patients in the cohort without GI symptoms (> 75 years old, n=16) compared to male patients in the cohort of GI symptoms (> 75 years old, n=3) (Figure 1).

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Figure 1: Risk of clinical outcomes A) respiratory failure, B) hospitalization and C) mortality among COVID-19 male and female patients presented with or without GI symptoms.

	Covid-19 with no GI symptoms	Covid-19 with GI symptoms		
	NO GI symptoms	**With GI symptoms**	**Measure of Association**	
	Male	**Female**	**Male**	**Female**
No. of patients (n or %)	80/170 (47%)	90/170 (53%)	20/50 (40%)	30/50 (60%)
Mean age	57.1±19.1	55.3±13.7	47.9±20.3	51.9±19.9
Race* (%)				
White	62%	66%	50%	66%
African American black	12%	11%	50%	33%
Asian	12%	11%	50%	33%
Unknown	25%	22%	50%	33%
Others	12%	11%	0%	33%

Table 1: Comparison of patient Demographics among COVID-19 male and female patients.
*TriNetX platform rounds patient counts in analyses up to the nearest 10. (Percentage may add up to more than 100%).

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OUTCOMES	Patients with outcomes	Patients with outcomes	Risk Ratio (95% confidence interval)	Risk difference (95% confidence interval)	P-Value
Males					
Respiratory Failure	50/80 (62.5%)	20/20 (100%)	0.625 (0.527, 0.741)	-37.5% (-48.109, -26.89%)	0.0011
Hospitalization	50/80 (62.5%)	20/20 (100%)	0.625 (0.527, 0.741)	-37.5% (-48.109, -26.89%)	0.0011
Mortality	10/80 (12.5%)	0/20 (0%)	0	12.50%	0.0956
Females					
Respiratory Failure	40/90 (44.44%)	20/30 (66.667%)	0.667 (0.473,0.939)	-22.22% (-41.97, -2.475%)	0.035
Hospitalization	40/90 (44.44%)	20/30 (66.667%)	0.667 (0.473,0.939)	-22.22% (-41.97, -2.475%)	0.035
Mortality	0/90 (0%)	0/30 (0%)	0	0%	0

Table 2: Outcomes among COVID-19 male and female patients presented with or without GI symptoms.

Discussion

GI symptoms are common in patients with COVID-19 as reported previously [7,8]. Our study aimed to characterize the clinical outcomes of COVID-19 patients with GI symptoms and evaluated differences in chosen outcomes between male and female patients. Although the prevalence of females with GI symptoms (25%) in our study was higher than males (20%), males showed a higher risk of poor clinical outcomes, including respiratory failure and hospitalization. We postulate that the gender-related difference in GI symptoms can be explained on the basis of behavioral, hormonal or immunological factors. However, the exact reason for the difference remains elusive. The relative risk of adverse outcomes was markedly higher in male patients than female patients, consistent with recent published reports [9,10]. Respiratory failure and hospitalization were seen in the vast majority of male patients with GI symptoms as compared to male patients without GI symptoms (RR 0.625, 95% CI 0.527-0.741, p-value-0.0011), suggestive of the presence of SARS-CoV-2 in intestinal tissues. This may be due to the high expression of angiotensin converting enzyme-2 (ACE-2) receptor in intestinal epithelial cells, as well as in the lung tissues, which has been reported to be the main host cell receptor of SARS-CoV-2 [11,12]. Additionally, mounting of the Th2 immune responses by SARS-CoV-2 may also contribute to GI symptoms, as has been recently suggested [13]. Gastrointestinal symptoms in COVID-19 patients are significantly associated with dyspnea, which is linked to a Th2 response [13,14]. Moreover, the GI common symptoms may be an indication of defective intestinal barrier, which leads to bacterial translocation and exacerbating systemic infection and inflammation.

The relatively low local mortality rate of COVID-19 patients independent of GI symptoms and gender is difficult to explain. We postulate that the low local prevalence rates and perhaps easier access to hospitalization and intensive care support may have resulted in patients seen earlier in the course of disease. In addition, a unique contact tracing program utilizing Penn State Hershey Medical Students under faculty supervision and supported by a dedicated COVID-19 clinic was implemented.

Conclusion

Our study is limited by the smaller sample size, is from a single center and results may not be generalizable. However, it provides the unique perspective of the impact of disease related factors in a low prevalence area with low population density. Further, multi-institutional larger studies are needed to validate these findings.

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Disclosure

Shannon Dalessio, Steven King, Iryna Pinchuk and Rana

Al-Sadi declare that they have no conflict of interest.

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