The Association between ADHD and the Severity of COVID-19 Infection

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Abstract

Objective: Patients with ADHD are at increased risk of acquiring COVID-19. The present study assessed the possibility that ADHD also increases the risk of severe COVID-19 infection. **Method:** We assessed 1,870 COVID-19 positive patients, aged 5 to 60 years, registered in the database of Leumit Health Services (LHS, Israel), February to -June 2020, of whom 231 with ADHD. Logistic regression analysis models evaluated the association between ADHD and the dependent variables of being symptomatic/referral to hospitalization, controlling for demographic and medical variables. **Results:** Age, male sex, and BMI were confirmed to be significant risk factors for increased COVID-19 severity. ADHD was found to be associated with increased severity of COVID-19 symptoms (OR = 1.81, 95% CI [1.29, 2.52], $p < .05$) and referral to hospitalization (OR = 1.93, 95% CI [1.06, 3.51], $p = .03$). **Conclusion:** ADHD is associated with poorer outcomes in COVID-19 infection. (*J. of Att. Dis. 2022; 26(4) 491-501*)

Keywords

ADHD, COVID-19, symptom severity, referral to hospitalization

Introduction

The COVID-19 pandemic has been associated with a global healthcare crisis. One of the unique features of the COVID-19 pandemic has been the extraordinary interindividual variability in presentation. Between 30% and 58% of COVID-19 infections are asymptomatic (Oran & Topol, 2020; Pollán et al., 2020; Sakurai et al., 2020), and a majority of patients present with a mild self-limited respiratory disease. At the other end of the spectrum, as of December 13th, 2020 COVID-19 has also led to 1.59 million deaths worldwide and the death toll continues to increase dramatically (Verity et al., 2020; World Health Organization, 2020; Wu & McGoogan, 2020). Identification of risk factors for disease severity is critical to identify those who may require priority in testing, close observation, early treatment, or hospitalization and who should be prioritized for possible vaccination. Given this variability in severity and the possible dramatic course of sudden deterioration, research into predictors of COVID-19 severity is critical to improve prevention efforts and to optimize health service delivery (Adams et al., 2020). This becomes even more significant as the strain in health care resources requires prioritizing levels of care.

Known predictors of severity of COVID-19 illness include advanced age, male sex, cardiovascular disease (CVD), diabetes mellitus (DM) (Williamson et al., 2020), hypertension (HTN) (Deng et al., 2020), chronic obstructive pulmonary

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disease (COPD), cancer (Liang et al., 2020), chronic kidney disease (CKD), smoking (Reddy et al., 2021) and obesity (BMI >30 Kg/m^2) (Petrilli et al., 2020; Williamson et al., 2020; Zheng et al., 2020). Epidemiological research in the United States (US) has also shown an increased risk of severe outcomes for disadvantaged populations, including low income populations, people of color, Hispanics and aboriginal populations (Alcendor, 2020).

Patients with mental illness in general are a high-risk population for medical conditions, (Cortese et al., 2020) raising the question of whether they may also suffer significantly worse outcomes due to COVID-19. Indeed, psychiatric populations in general are known to be high risk for adverse outcomes of infection. For instance, a large population study in Denmark suggested that a diagnosis of depression was associated with a higher 30-day mortality for those hospitalized with an infection (Davydow et al., 2016). This also appears true for COVID-19. For example, a psychiatric diagnosis for patients hospitalized with COVID-19 was linked to a 1.5-fold increased risk of a COVID-19-related death in comparison with COVID-19 patients who had not received a psychiatric diagnosis (Li et al., 2020). Additionally, a large analysis of US electronic health records concluded that a recent diagnosis of a mental disorder, including ADHD, was associated with both increased infection rates and increased morbidity and mortality from COVID-19 (Wang et al., 2021).

ADHD is a common disorder with an estimated worldwide pooled prevalence of between 5% and 7.5% in school aged children (Cortese & Coghill, 2018) and 4.4% in adults (Kooij et al., 2016), although ADHD might be underdiagnosed in the adult population. ADHD is less likely to be recognized or diagnosed in the preschool (Childress & Stark, 2018) or geriatric population (Kooij et al., 2016; Ojo et al., 2020). ADHD is associated with significant impairment (Simon et al., 2009), poor self-care, and other health conditions, such as sleep disorders (Cortese et al., 2009), obesity (Cortese et al., 2016) or asthma (Cortese et al., 2018) which could lead to increased risk for deleterious COVID-19 outcomes. Adverse outcomes adults with ADHD include smoking, drug use, accidents, poor diabetes control and shortened life span (Vinker-Shuster et al., 2019). ADHD would therefore be predicted to be associated with poor COVID-19 outcome, even if only by association with other clinical correlates. Given the extent to which ADHD patients are a high-risk group on many other known and unknown variables, it may even be possible that ADHD may predict poor COVID-19 outcomes. Previous research demonstrated that untreated ADHD is a risk factor for acquiring COVID-19 (Merzon et al., 2020; Wang et al., 2021), further suggesting the possibility that ADHD might also be a risk factor for severity of COVID-19 symptoms, but so far evidence supporting this claim is limited Indeed, in a recent large national US study of electronic health records Wang et al. (2021), found an increased risk of acquiring COVID-19 in individuals with ADHD (adjusted odds ratio: 7.31, 95% CI [6.78, 7.87], $p < .001$). However, this study did not explore relative risk for death or hospitalization specific to ADHD. The study was also limited to adults older than 18 years and only 0.2% or 220 patients were described as having a recent diagnosis of ADHD, which suggests that that ADHD diagnosis was underrepresented. Given these findings suggestive of mental illness as a possible risk factor for poor COVID-19 outcome, the objective of the study reported here was to determine if ADHD is an independent risk factor for symptomatology and hospitalization with COVID-19.

We hypothesized that ADHD diagnosis would be associated with severity of COVID-19 symptoms and referral for hospitalization.

Methods

Participants and Procedures

Participants ($N = 1,870$) were drawn from a database of patients serviced by the Leumit Health Services (LHS) in Israel, which is continuously updated in relation to subjects' demographics, medical visits, laboratory tests, medication prescriptions and hospitalizations. The study was conducted between February 1st and June 30th, 2020. The study population included all the COVID-19 positive (COVID-19+) patients. All study participants had similar health insurance and similar access to health services. Data were collected from the LHS computerized database, including demographics for the entire cohort. Socioeconomic status (SES) was coded based on the patient's home address, using the Israeli Central Bureau of Statistics' classification, which includes 20 subgroups, with groups 1 to 10 classified as low-medium SES and groups 10 to 20 as high SES. The electronic health record (EHR) and database includes whether participants reported smoking, or were diagnosed with obesity, asthma, chronic obstructive lung disease (COPD), diabetes mellitus (DM), hypertension, and various other chronic medical diagnoses. Participants were limited to age range of 5 to 60-year-old since this is the group which can be most reliably diagnosed with ADHD (Dobrosavljevic et al., 2020).

Psychiatric diagnoses in the EHR included depression/anxiety and schizophrenia as per the International Classification of Disease, ninth revision (ICD-9) or tenth revision (ICD-10) codes. A limitation of the EHR was that depression and anxiety were combined together as one entity, thus depression and anxiety were not differentiated in the EHR to separate clinical entities.

Diagnosis of ADHD was based on the American Psychiatric Association's Diagnostic and Statistical Manuals 4th or 5th edition, depending on the date of ADHD assessment. Diagnosis was established by senior physicians, specializing in ADHD, which is the standard of care for assessment in Israel. These clinicians include child or adult psychiatrists, child or adult neurologists, or pediatricians and family physicians with certified ADHD training based on Spitzer's LEAD criteria (L=Longitudinal evaluation of symptomatology, E=Evaluation by expert consensus, AD=All Data from multiple sources) which has been shown to be as reliable as structured interviews (Miller et al., 2001). Of note, access to diagnosis of ADHD in Israel is equitably distributed across all age groups, although referral may be limited by decreased recognition of ADHD in adults. The number of participants with ADHD was 231.

Referral for COVID-19 testing was made at the discretion of the primary care physician (PCP) according to the Israeli Ministry of Health's criteria: direct, close unprotected exposure to a confirmed COVID-19 positive (COVID-19+) patient and/or presenting symptoms suggesting COVID-19 infection. Testing was performed with nasopharyngeal swabs evaluated for COVID-19 by an RT-PCR assay with internal positive and negative controls according to the guidelines of the World Health Organization. The Allplex™ 2019-nCoV Assay (Seegene Inc., Seoul, Republic of Korea) was used until March 10th, 2020, and since then—the COBAS SARS-Cov-2 6800/8800 (Roche Pharmaceuticals, Switzerland).

All COVID-19+ patients underwent a telephone intake and triage by a board-certified physician on the day of receiving a positive test result, and the need for hospitalization was determined according to subjective assessment, based on a checklist of symptoms severity (Appendix 1). This checklist was updated during these months according to the changing instructions of the Israeli Health Ministry, based on WHO's instructions.

We selected confounders based on research establishing known risk factors for poor COVID-19 outcome, which include demographic variables such as age, sex and SES, high risk behaviors such as smoking and pre-existing medical conditions. Age was found to be the strongest risk factor for severity as was measured by hospitalization (Petrilli et al., 2020; Williamson et al., 2020). Chronic heart disease, BMI >40 and male sex were also found to be risk factors for critical outcomes besides age (Petrilli et al., 2020; Williamson et al., 2020). Smoking was found as an increased risk for critical outcome for both current smokers and for patients with a smoking history (Reddy et al., 2021). Other risk factors that were found to be associated with the severity of COVID-19 were diabetes mellitus (DM), COPD, and asthma (Williamson et al., 2020). Hypertension was also reported to be a risk factor alongside the male sex, DM, COPD, and CHD (Deng et al., 2020). In their above mentioned study about mental disorders, Wang et al. (2021) reported that depression and schizophrenia, as well as SES level were also a risk factor for severity.

Statistical analysis

Descriptive statistics were used to report demographic characteristics between the study groups. The relationship between demographics and COVID-19 was evaluated using *t-test* and Fischer exact/χ^2 test for continuous and categorical variables, respectively, based on normal distribution and variable characteristics. Preliminary evaluation of association between ADHD diagnosis and the severity of COVID-19 was conducted by stratified analyses. Subsequently, to estimate severity, as reflected by the existence of symptoms and by referral to hospitalization, we used two multivariate logistic regression models. Thus, an evaluation of the odds ratios (*OR*) and 95% confidence interval (CI) for the independent association between both factors and ADHD diagnosis was done while controlling potential confounders. A sample size of 1,870 gave the study approximately 80% power to detect at least 5% higher prevalence of ADHD among COVID-19 positive patients as compared with COVID-19 negative.

The study protocol was approved by the Shamir Medical Center Review Board and the Research Committee of LHS (0129-20-LEU-31.5.2020).

Results

Demographics

The population of this study included 1,870 COVID-19 positive patients. Mean age was 29.03 (*SD*=14.80 years), distributed as 32.2% <20 years, 40.5% 21 to 40 years, and 27.3% >40 years. 82.6% were from low-medium SES levels and 52.7% were male. Prevalence of medical comorbidities included: obesity 17.6%, diabetes mellitus (DM), 4.4%, hypertension (HTN) 5.5%, cardiovascular disease (CVD) 2.2%, chronic obstructive pulmonary disease (COPD) 0.3%, smoking 4.7%, and asthma 6.5%. Prevalence of psychiatric comorbidities included: ADHD 12.4%, depression 2.2%, and schizophrenia 1.2%. The high percentage of ADHD patients is in accordance with findings in former studies (Merzon et al., 2020; Wang et al., 2021) indicating that ADHD is a risk factor for being infected by COVID-19.

Symptomatic Status

There were significant differences between the symptomatic and asymptomatic patients. The asymptomatic patients were significantly younger, tended to be female, and had lower BMI (Table 1). The SES distribution was similar in the two groups. Among symptomatic patients the following chronic health disorders were more prevalent: obesity, CVD, DM, and HTN (Table 2).

Symptomatic status was also compared across ADHD diagnosis. Individuals with ADHD were significantly more likely to be symptomatic. The prominent symptoms that

Table 1. Demographic Characteristics of the COVID-19 Positive Patients (Total Population: $N = 1{,}870$) Divided by Symptom Presentation and Referral for Hospitalization.

	Symptoms			Hospitalization		
	Yes	No		Yes	No	
Variable	*M (SD)/n* (%)	*M (SD)/n* (%)	t/χ^2	*M (SD)/n* (%)	*M (SD)/n* (%)	t/χ^2
n	737 (39.4)	1,133 (60.6)		117 (6.3)	1,753 (93.7)	
Age (years)	32.6 ± 14.6	26.7 ± 14.4	−8.64**	36.4 ± 14.9	28.6 ± 14.7	−5.61**
SES[a]						
Low-medium	591 (87.0)	954 (90.0)	1.91	93 (79.5)	1,452 (82.8)	1.75
High	88 (13.0)	106 (10.0)		18 (15.4)	176 (10.0)	
Gender						
Male	424 (47.5)	561 (49.5)	−3.39**	74 (63.3)	911 (52.0)	−2.37*
Female	313 (42.5)	572 (50.5)		43 (36.8)	842 (48.0)	
BMI,[b] Kg/m^2	26.3 ± 6.5	24.1 ± 6.5	−6.34**	26.9 ± 6.7	24.8 ± 6.5	−3.34**

Note. SES = socioeconomic status; BMI = body mass index.
[a]SES missing data for any symptoms group is 21 (9%) and for non-symptoms group 73 (6.4%).
[b]BMI missing data for any group is 28%.
*$p < .05$. **$p < .01$.

Table 2. Distribution of Mental and Physical Diagnoses of the COVID-19+ Patients, Divided by: Symptom Presentation and Patients Referred to Hospitalization.

		Symptoms			Hospitalizations		
		Yes	No		Yes	No	
	Total	*n* (%)	*n* (%)	χ^2	*n* (%)	*n* (%)	χ^2
n (%)	1,870	737 (39.4)	1,133 (60.6)		117 (6.3)	1,753 (93.7)	
ADHD	231 (12.4)	105 (14.2)	126 (11.1)	−2.01*	22 (18.8)	209 (11.9)	−2.19*
Depression/anxiety	42 (2.2)	22 (2.3)	20 (1.8)	−1.74	7 (6.0)	35 (2.0)	−2.82**
Schizophrenia	23 (1.2)	15 (2.0)	8 (0.7)	−2.55*	5 (4.3)	18 (1.0)	−3.09**
Obesity[a]	330 (17.6)	166 (22.5)	164 (14.5)	−4.25***	31 (26.5)	299 (17.1)	−2.15**
Diabetes mellitus	82 (4.4)	52 (7.1)	30 (2.6)	−4.55***	18 (15.4)	64 (3.7)	−6.00***
Hypertension	102 (5.5)	55 (7.5)	47 (4.1)	−3.08**	15 (12.8)	87 (5.0)	−3.62***
CVD	53 (2.2)	33 (4.2)	20 (1.8)	−3.45***	12 (10.3)	38 (2.2)	−3.85***
COPD	6 (0.3)	4 (0.5)	2 (0.2)	0.170	2 (1.7)	4 (0.2)	0.006
Asthma	123 (6.5)	34 (4.6)	89 (7.9)	2.76**	8 (6.8)	115 (6.5)	−0.12
Smoking	88 (4.7)	37 (5.0)	51 (4.5)	−0.52	7 (6.0%)	81 (4.6)	−0.67

Note. ADHD = attention deficit hyperactivity disorder; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease.
[a]Obesity: BMI ≥ 30, 28% missing data.
*$p < .05$. **$p < .01$. ***$p < .001$.

differed significantly between ADHD and non-ADHD symptomatic patients were fever (above 38 °C), and presence of suspected pneumonia (Table 3).

A multiple logistic regression analysis for symptomatic presentation was conducted controlling for the demographic and clinical comorbidities (Table 4). Significant associations included being a male ($OR = 1.34$, 95% CI [1.07, 1.68], $p < .05$), age ($OR = 1.02$, 95% CI [1.01, 1.03], $p < .001$), and having ADHD ($OR = 1.81$, 95% CI [1.29, 2.52], $p < .05$). ADHD was the only significant predictor among the mental and physical disorders.

Hospitalization Rates

One hundred and seventeen COVID-19+ patients (6.2%) were hospitalized. Referral to hospitalization was significantly associated with older age, male, and high BMI (Table 1). Hospitalization was also significantly correlated with HTN, DM, CVD, and obesity, but not asthma (Table 2). Among the psychiatric disorders, both schizophrenia and depression were associated with significantly increased rates of hospital referral. ADHD was also associated with a significantly higher rate of hospitalisation (Table 2).

Table 3. Distribution of Symptoms and Signs in the Study Population. (The Test is Chi Square, Except the Age, Which Was Analyzed by *t*-Test.).

Variable	Total	ADHD *n* (%)/*M* (*SD*)	Non-ADHD *n* (%)/*M* (*SD*)	t/χ^2
n (%)	1,870	231 (12.3)	1,639 (87.6)	
Age	29.03 ± 14.79	21.76 (10.18)	30.05 (15.06)	8.12***
Asymptomatic	1,133	126 (54.6)	1,007 (61.5)	2.01*
Symptomatic	737	105 (45.5)	632 (38.5)	−2.01*
Fever[a]	89	25 (23.8)	64 (10.1)	−3.98***
Pneumonia[b]	11	6 (5.7)	5 (0.6)	−4.17***
Anosmia	86	15 (14.3)	71 (11.2)	−0.90
URTI	456	43 (41.0)	413 (65.4)	5.39***
Gastrointestinal[c]	27	6 (5.7)	21 (3.3)	−1.21
Neurological[c]	69	10 (9.5)	59 (9.3)	−0.06

Note. ADHD = attention deficit hyperactivity disorder; URTI = upper respiratory tract infection.
[a]Fever: >38°C.
[b]Diagnosis of pneumonia based on symptoms, clinical examination and/or X-ray.
[c]Values reflect the percentage of a specific symptom out of 100% of symptomatic patients, ADHD or non-ADHD.
*$p < .05$. ***$p < .001$.

Table 4. Logistic Regression for Crude and Adjusted Odds Ratios for Symptomatic and Asymptomatic Patients, Demographic, and Clinical Characteristics.

Variable	Crude *OR*	Crude 95% CI [LL, UL]	*p*	Adjusted *OR*	Adjusted 95% CI [LL, UL]	*p*
ADHD	1.33	[1.01, 1.75]	.045*	1.81[a]	[1.29, 2.52]	.042*
Male gender	1.38	[1.14, 1.66]	.001**	1.34	[1.07, 1.68]	.012*
Age[b]	1.02	[1.02, 1.03]	.000***	1.02	[1.01, 1.03]	.000***
Low-medium SES	0.74	[0.55, 1.01]	.056	0.91	[0.64, 1.31]	.634
Depression/anxiety	1.71	[0.93, 3.16]	.085	0.82	[0.40, 1.71]	.607
Schizophrenia	2.92	[1.23, 6.92]	.015*	1.81	[0.74, 4.71]	.181
Diabetes mellitus	2.79	[1.76, 4.42]	.000***	1.61	[0.96, 2.73]	.070
Hypertension	1.86	[1.25, 2.78]	.002**	1.06	[0.65, 1.71]	.24
CVD	2.61	[1.48, 4.58]	.001**	1.41	[0.74, 2.67]	.293
COPD	3.09	[0.56, 16.89]	.194	1.46	[0.19, 10.87]	.710
Obesity	1.70	[1.33, 2.18]	.000***	1.25	[0.94, 1.66]	.121
Smoking	1.31	[0.59, 2.91]	.502	0.88	[0.53, 1.46]	.634

Note. CI = confidence interval; LL = lower limit; UL = upper limit; ADHD = attention deficit hyperactivity disorder; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; SES = socioeconomic status.
[a]Without age, *OR* for ADHD = 1.6, 95% CI [1.15, 2.2].
[b]Age was included as a continuous variable.
*$p < .05$. **$p < .01$. ***$p < .001$.

A multiple logistic regression analysis for hospitalization was conducted controlling for demographic variables and comorbidities (Table 5). When adjusted ORs were calculated, several factors were found to be significant: CVD ($OR = 2.71$, 95% CI [1.09, 6.73], $p < .05$), DM ($OR = 2.23$, 95% CI [1.11, 4.47], $p < .01$), ADHD ($OR = 1.93$, 95% CI [1.06, 3.51], $p < .05$), and age ($OR = 1.02$, 95% CI [1.01, 1.04], $p < .01$). It should be noted that every year of age increases the likelihood to be referred for hospitalization by 2%. Notably, within the current sample of ADHD patients, the presence of allergic/autoimmune diseases and smoking status did not affect the presence of symptoms or the rate of referral to hospitalization (data available upon request).

Post-hoc analysis of age as a categorical variable

Due to the significant effect of age we conducted a sub-analysis of the effect of age, as a categorical variable, on COVID-19+ severity in the total study population divided to three groups: 5 to 20 years old ($n = 607$), 21 to 40 years

Table 5. Logistic Regression for Crude and Adjusted Odds Ratios for Patients Referred to Hospitalization, Demographic, and Clinical Characteristics.

	Crude *OR*			Adjusted *OR*		
Variable	*OR*	95% CI [LL, UL]	*p*	*OR*	95% CI [LL, UL]	*p*
Diabetes mellitus	4.80	[2.74, 8.41]	.000 ***	2.23	[1.11, 4.47]	.024 *
CVD	4.48	[2.09, 9.63]	.000***	2.15	[1.09, 6.73]	.032 *
ADHD	1.71	[1.05, 2.78]	.030*	1.93[a]	[1.06, 3.51]	.030 *
Age[b]	1.03	[1.02, 1.05]	.000***	1.02	[1.01, 1.04]	.009**
Male gender	1.59	[1.08, 2.34]	.019*	1.39	[0.88, 2.18]	.155
Low-medium SES	0.63	[0.37, 1.06]	.083	0.80	[0.43, 1.48]	.479
Depression/anxiety	3.12	[1.36, 7.19]	.007**	2.53	[0.99, 6.50]	.053
Schizophrenia	4.30	[1.57, 11.80]	.005**	2.02	[0.61, 6.75]	.253
Hypertension	2.82	[1.57, 5.05]	.001**	1.50	[0.75, 3.01]	.255
Asthma	1.05	[0.50, 2.20]	.907	0.78	[0.32, 1.90]	.590
COPD	7.60	[1.38, 41.95]	.020*	4.87	[0.50, 47.78]	.174
Obesity	1.62	[1.04, 2.53]	.033*	0.96	[0.57, 1.60]	.867
Smoking	1.31	[0.59, 2.91]	.502	0.78	[0.31, 2.01]	.613

Note. CI = confidence interval; LL = lower limit; UL = upper limit; ADHD = attention deficit hyperactivity disorder; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; SES = socioeconomic status.
[a]Without age *OR* for ADHD = 1.59, 95% CI [0.96, 2.83].
[b]Age was included as a continuous variable.
*p < .05. **p < .01. ***p < .001.

Table 6. Post-Hoc Analysis of Age Effect in ADHD Patients Using Mantel-Hanzel.

		Symptomatic			Hospitalizations		
Age (years)	*n*	*OR*	95% CI [LL, UL]	M-H	*OR*	95% CI [LL, UL]	M-H
5–20	111	3.31	[2.09, 5.21]	$\chi^2 = 9.02$, $p < .01$	1.64 (NS)	[0.37, 5.67]	$\chi^2 = 13.51$, $p < .001$
21–40	111	0.79	[0.51, 1.23]		2.96	[1.40, 5.93]	
41–60	17	1.53	[0.51, 4.64]		2.56	[0.60, 8.99]	

Note. ADHD = attention deficit hyperactivity disorder; M-H = Mantel-Hanzel; CI = confidence interval; LL = lower limit; UL = upper limit.

old ($n = 758$), 41 to 60 years old ($n = 505$). Both groups of adults (21–40, 41–60 years) exhibited higher rates of symptomatic status ($OR = 2.84$, 95% CI [2.23, 3.61], $\chi^2 = 79.76$ and $OR = 2.23$, 95% CI [1.73, 3.00], $\chi^2 = 39.11$, respectively, $p < .001$ for both) compared to children and adolescents. The same was true for referral to hospitalization status ($OR = 2.61$, 95% CI [1.44, 4.73], $\chi^2 = 10.80$ and $OR = 4.82$, 95% CI [2.67, 8.73], $\chi^2 = 33.10$, respectively, $p < .001$ for both) compared to children and adolescents.

In addition, we conducted a post-hoc analysis examining differences in the association between age and ADHD with symptomatic status and referral to hospitalization status, using the Mantel-Hanzel method (Table 6).

Two hundred and thirty-one COVID-19+ patients were diagnosed with ADHD. They were analyzed categorically divided to the same age groups, 5 to 20 years ($n = 111$), 21 to 40 years ($n = 111$), 41 to 60 years old, ($n = 17$). The young ADHD age group (5-20 years) revealed significantly higher rate of symptomatic status, compared to the non-ADHD children and adolescents (adjusted $OR = 3.22$ 95% CI [2.04, 5.09], $p < .001$). Such difference was not demonstrated for being referred to hospitalization. This insignificance may be related to the small number ($n = 15$) of hospitalized children and adolescents (adjusted $OR = 1.54$ 95% CI [0.47, 5.03], $p = .475$).

In the older age groups (21–40, 41–60 years), having ADHD was associated with higher rates of referral to hospitalization (Table 6). No significant difference was observed with regard to the symptomatic status.

Discussion

The aim of this study was to assess in COVID-19 infected subjects the association between ADHD and the severity of COVID-19 infection, as was defined by an increased risk of being symptomatic, suffering from greater symptom severity and being referred to hospitalization after controlling for possible confounding factors, including demographic, medical, psychiatric, and lifestyle variables. In addition to replicate previous findings demonstrating that age, obesity and chronic medical conditions are risk factors for COVID-19 symptom severity and hospitalization (Petrilli et al., 2020; Williamson et al., 2020; Zheng et al., 2020), we found that that having COVID-19 infection in patients with ADHD was associated with more severe symptoms and an increased rate of referral to hospitalization, even after accounting for variables known to increase the risk for both disorders. It is of note, that in this cohort, ADHD was as a strong predictor for COVID illness as diabetes mellitus and cardiovascular diseases, and much stronger than obesity or asthma. It is suggested that ADHD is by itself a risk factor for severity of COVID-19 illness.

To our knowledge, the only other empirical study of the association between ADHD and severity of COVID-19+ outcome is the Wang et al. (2021) study. They replicated our finding that ADHD is a risk factor for acquiring COVID-19 infection, but did not explore the relationship between ADHD and the severity of COVID-19 infection. Methodological differences between the two studies may explain some of the discrepancies in the results. Our sample included a younger population (29.03 + 14.80 years), and the age range was restricted to 5 to 60 years, whereas the Wang et al. (2021) study included only adults, with 29% of the sample older than 65 years. Given the lower prevalence of ADHD in adults, and even lower prevalence of ADHD in the geriatric population (Kooij et al., 2016; Ojo et al., 2020), it is not surprising that the Wang et al. (2021) study found only 1.7% of the patient population had lifetime ADHD, and only 0.7% had current ADHD, well below the known prevalence of the disorder. In our sample 12.4% of COVID-19+ patients had ADHD, consistent with the known world prevalence of the disorder and supporting the finding of overrepresentation of ADHD in a COVID-19+ sample (Merzon et al., 2020).. This study explored benign and common outcomes (COVID-19 symptoms and referral to hospitalization) and there is a need to explore a more severe outcome (need for respiration and mortality). Similar to previous studies, we found that older age is associated with the likelihood of being symptomatic and of being referred to hospitalization. However, in the youngest age group in our sample (5–20 years), in patients with ADHD, the OR for being symptomatic was 3.31 compared to the non-ADHD patients (Table 6). In this age group the referral to hospitalization was not associated with having ADHD, most probably due to the small sample size of ADHD patients ($n = 15$). Such a significant association between having ADHD and being referred to hospitalization was found in the 21 to 40 years group, but disappeared in the age group of 41 to 60 years, maybe due to the low rate of ADHD in this group, as well as the common presence of other significant risk factors. Clearly, age is a potent risk factor for negative outcomes, as are pre-existing conditions, but while youth may be at a lesser risk, they are not immune from risk.

Specific characteristics of ADHD in particular may be hypothesized to drive increased risk for severe COVID-19 outcomes. ADHD patients may be less likely to practice appropriate self-care, to seek medical attention, or to remain at home. It is also possible that COVID-19 severity is related to the exposed viral load (Fajnzylber et al., 2020), and that ADHD patients put themselves in high risk situations, as well as being inattentive and impulsive, which might explain the elevated probability of exposure that expose them to a higher viral load, thus to suffer from more symptoms and having higher risk to be referred to hospitalization.

It was also suggested that common biological factors for serious mental illnesses and COVID-19 such as inflammation may be involved (Cortese et al., 2019; Li et al., 2020).

Strengths and Limitations

The strengths of the study include the fact that data were drawn from a clinical community, during the first wave in which only high-risk patients were being referred for COVID-19 screening. Our sample size was sufficient to be able to control for several demographic and health variables that might otherwise explain the increased relative risk of ADHD to severe COVID-19 illness. Another strength of the sample is the inclusion of a wide spectrum of ages, including children, youth and young adults where ADHD is most common and is more commonly diagnosed.

Notably, this study was done in Israel, providing an important comparison with studies of COVID-19 patients' vulnerability in the United States. The median age of the population in Israel is 30.5 years, while in the United States it is 38.3 years, providing a better understanding of the relative risk in a younger population (Worldometers.info, 2020a, 2020b). Other differences between Israel and the US may have impacted our findings including greater homogeneity in race, access to health care and paid sick days. These between-country differences and our grouping low and moderate SES together, may together explain the relative lack of impact of SES in our study.

Limitations

The population in this study was relatively homogenous and so we were not able to differentiate effects of race. This may limit generalization to other settings. In addition, our measure of socioeconomic status did not differentiate poverty but mixed lower- and middle-class patients into one group. Our findings might not generalize to other settings. The diagnosis of ADHD in Israel is done by senior clinicians who are specialists in neurodevelopmental disorders using longitudinal, expert evaluation, in accordance to international recommendations, which is is typical in a majority of countries and health care systems. However, it could also limit generalization.

The use of EHR data has inherent limitations in differentiating current and past conditions, and in the accuracy of the data recorded. In addition, the EHR combined depression/anxiety as one entity.

A potential limitation of this study was underrepresentation of depression, given that we found a point prevalence of depression of 2%, while prevalence of depression in Israel is 4.6% (World Health Organization, 2017).This discrepancy may be related to the inclusion of children and youth who may be under diagnosed, and to the fact that anxious or depressed patients tended to avoid visits with their physicians during the pandemic. Alternatively, this may be a limitation of a community-based EHR study in which clinicians were reluctant to document depression and anxiety, especially during a pandemic. This possibility is consistent with the observation that in our sample COPD and schizophrenia clinical groups also included a very small number of patients, decreasing the likelihood of an association with COVID-19.

Noteworthy, the findings from this study are correlational, not causal, and need to be validated and confirmed in other databases or populations.

The telephone triage of patients was done at a single point in time, and so some patients with ADHD may have developed COVID-19 symptoms later on, possibly leading to underestimation of the strength of the association.

The sample size of 231 COVID-19 infected ADHD patients, may have limited the power of our ADHD analyses, given the number of variables. Triage for symptom severity and referral for hospitalization was based on the patient's report in a telephone interview, rather than direct clinical examination. There may be unknown variables impacting the association of ADHD with poor COVID-19 outcomes that are not included in our analyses..

Implications

This study raises the awareness of the increased risk of patients with ADHD to develop symptomatic COVID-19 clinical picture that may require referral to hospitalization. Clinicians aware of this association should practice a higher degree of vigilance not only in screening for COVID-19 infection in individuals with ADHD, but also in monitoring outcome, and providing a prompt effective treatment for the COVID-19 symptoms in this population. Overall, this study will contribute to provide evidence that can inform clinical guidance on the links between ADHD and COVID-19, whoch so far has derived mostly from expert consensus rather than empirical evidence (Cortese et al., 2020).

Conclusions

ADHD was found to be associated with an increased risk of symptomatic COVID-19+ and higher rates of referral to hospitalization over and above other known risk factors. Clinicians should be aware of the increased need for vigilance in caring for ADHD patients who are COVID-19 positive. Future research is needed to evaluate whether ADHD is a risk factor for longer duration of symptomatic COVID-19, and whether antecedent ADHD and/or other neurodevelopmental disorders are risk factors for neuropsychiatric sequelae from COVID-19 infection.

Appendix 1: Clinical Conditions

People with COVID-19 have had a wide range of symptoms reported—ranging from asymptomatic to severe ill. Symptoms may appear 2 to 14 days after exposure to the virus. People with COVID-19 may suffer from these symptoms. Do you have (Yes/No)?:

- Fever >38°C
- Cough
- Sore throat
- Shortness of breath or difficulty breathing
- Chills
- Headache
- Muscle or body aches
- New loss of taste or smell
- Nausea or vomiting
- Abdominal Pain
- Diarrhea

This list does not include all possible symptoms. CDC will continue to update this list as we learn more about COVID-19.

Underlying Medical Conditions Needed Special Attention (Yes/No):

Cardiovascular Disease
Diabetes Mellitus
Hypertension
Pregnancy
Depression of immune system
Choric lung diseases (COPD, Asthma)
Choric lever disease:
Other chronic disorders (specify) ____________________

Author Note

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