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The Comparison of Clinical Characteristics of PCR confirmed COVID-19 (SARS-CoV-2 infection) cases in different age groups.

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Abstract
Purpose of Study and Research Objectives: *1. To aggregate data on PCR confirmed cases of SARS-CoV-2 infection to clearly identify the clinical characteristics of COVID-19 disease in different age groups. 2. To determine if there are any differences in the clinical presentation of COVID-19 in Children, Adults and Older Adults.3.To review published literature on (i) why some are more susceptible than others to severe infection and outcome (ii) what are the long term-effects of SARS-CoV-2 infection.*
Method: *One database search (PubMed, Medline) was conducted using only PCR-confirmed cases of SARS-CoV-2 infections to collect data on the clinical manifestations of COVID-19reported from 2019-2021. Data was extracted from the results, figures and tables of studies which met the selection criteria. Studies unavailable in English, without PCR confirmed cases and which combined the symptoms of children and adults were excluded.*
Main outcome measure: *The frequency of each reported COVID-19 symptom in different age groups.*

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I. Introduction

The initial outbreak of COVID-19 disease (SARS-CoV-2 infection) was first reported on December 31st 2019 in Wuhan China, and was officially declared a pandemic by the World Health Organization (WHO) on March 11th 2020 (WHO, 2020). At the end of the second year of the ongoing pandemic the number of lives that have been claimed worldwide to date is 5,374,744, with the total number of confirmed cases at 276,436,619, and the number of new cases in last 24 hours is 822,278 as of December 23rd, 2021 (WHO, 2021b); with the number still rising and novel strains with increased transmissibility emerging, such as the delta (B.1.617.2) variant in October 2020 and more recently the Omicron (B.1.1.529) variant in November 2021 (WHO, 2021c). The Americas have the highest number of confirmed cases worldwide at 100,567,882 cases, followed by Europe at 96,066,316 cases, South-East Asia at 44,865,441 cases, Eastern Mediterranean at 17,060,248 cases, the Western Pacific at 10,951,127 and Africa at 6,924,841 confirmed cases as of December 23rd 2021 (WHO, 2021b).

Worldwide, a total of seven vaccines have been distributed. The approved vaccines being distributed in the United States are Pfizer-BioNTech (2 shots, administered 21 days apart) for ages 12 and above, Moderna (2 shots, administered 28 days apart) for ages 18 and above, and Johnson & Johnson/ Janssen (1 shot) for ages 18 and above. For all three vaccines individuals are considered fully vaccinated 2 weeks after administration of the full vaccine dose (CDC, 2021b). In the United Kingdom, the 3 US approved vaccines are also approved for use in the UK as well as the Oxford/ AstraZeneca vaccine (2 shots) (NHS, 2021). In total, 8,649057088 vaccine doses having been administered worldwide as of December 23rd, 2021 (WHO, 2021b).In combination with this, as of December 22nd 2021 the U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorizations for Paxlovid (Nirmatrelvir and Ritonavir tablets) anti-viral tablets by Pfizer-BioNTech for use in adults and children aged 12 years and above in mild to moderate cases of COVID-19 disease to prevent progression to severe illness (FDA, 2021).

II. Materials and Methods

One database search (PubMed, Medline) was conducted in this study using only PCR-confirmed cases of SARS-CoV-2 infections to collect data on the clinical manifestations and presentations of COVID-19 disease reported to date (from 2019-2021). Search terms in PubMed were "Covid-19" OR "SARS-CoV-2" OR "COVID", AND "Clinical Presentation", OR "Symptoms" OR "Clinical manifestation", AND in "Children", OR "Adults" OR "Elderly" OR "Older" OR "Age".

Eligibility Criteria:

Once studies were identified for full review, they needed to meet the following eligibility criteria for selection:

1. PCR test confirmed cases of SARS-CoV-2 infection only.
2. Study language in English or available in English.
3. Data on children, adults and older adults were able to be extracted from the study. Studies where findings were combined with no means of identifying the ages of the reported symptoms were excluded (for example studies combining patients aged 0-88, and symptoms for those aged below 19, or above 65 could not be extracted from the data, were excluded).
4. Studies with significantly larger sample sizes (above n = 3000) were also excluded to maintain homogeneity and allow for studies of comparable sizes to be evaluated.

The total number of relevant studies identified and selected for review was 48, 12 of which were excluded as the symptoms of children and adults could not be separated as outlined in the eligibility criteria, and 1 study was excluded due to the sample size being significantly larger than the rest of the collected data set selected for evaluation (n = 10,955), leaving a total of 35 studies which were included in this investigation. The total sample size for the Children's group (0-19) was 2,475, for the Adults group (20-64) was 2,955, and Older Adults group (65+) was 3,561 (See Figure 1. PRISMA Flow Diagram in the Results Section).

The numbers reported for each symptom was extracted from the results sections, and data tables provided in each study. For each symptom the number reported was evaluated against the sample size of the studies that reported each symptom, studies where a symptom was not reported were not included in the evaluation of that symptom as it was unclear whether the lack of reporting of the figures for the symptom was because none of the participants experienced it making the figure 0, or whether participants did experience the symptom but it was not reported in the results section of the published data study.

III. Literature Review

A review of the published literature from 2019 to 2021, on the clinical characteristics and manifestations of COVID-19 reveals several different presentations ranging from asymptomatic to severe respiratory illness requiring ICU admission within days of having contracted the infection (Zhong, Z. *et al.*, 2021). In 2021, a Meta-Analysis by Zhu, J. *et al.* in 2020 was conducted across 7 databases with 3,062 patients which also aimed to identify the clinical characteristics of COVID-19 however, there has not been one more recently inclusive of patient data from 2021 as well as focusing on the distribution of clinical characteristics of COVID-19 by age group which is the purpose of conducting this study. A similar study which was Systematic Review and Meta-Analysis of COVID-19 symptoms in children by Cui, X. *et al.* in 2020 of 48 studies and a sample size of 5,829 patients found 20% of children to be asymptomatic in their presentation, 33% mild presentation of symptoms and 51% with a moderate presentation of symptom severity, their study concluded that children were more likely to have an atypical presentation and milder illness when infected with SARS-CoV-2 (Cui, X. *et al.*, 2020).

A study in the United States by the Centers for Disease Control and Prevention (CDC) COVID-19 Response Team of 10,944 adults aged 18-64, found that 93% of participants reported experiencing fever, cough, or shortness of breath in comparison to only 73% of pediatric patients in this study exhibiting the same symptoms (Bialek, S. *et al*., 2020). Another interesting study conducted in 2020 and published in 2021 by scientists with King's College London, Massachusetts General Hospital and the ZOE Symptom study app which analyzed data collected from 2,700 app users (self-reporting), revealed six distinct types of COVID-19 symptom clusters which also differ in severity of the illness. These six reported clusters were 1. Flu-like and non-febrile, 2. Flu-like and febrile, 3. Gastrointestinal, 4. Severe level one, fatigue, 5. Severe level two, confusion, 6. Severe level three, abdominal and respiratory. Within each cluster further symptoms common to all are reported these include headache, loss of smell, sore throat, cough, chest pain, loss of appetite (absent in clusters 1 and 4) and hoarseness (absent in clusters 1 and 3) (Sudre, C.H. *et al.*, 2021a). Overall, the review of the published literature highlights the need for clear identification of COVID-19 clinical presentation of confirmed cases of SARS-CoV-2 infection as it appears to differ between people and can easily be mistaken for influenza infection (Song, X. *et al.*, 2020). Another key objective of this review study is to determine if there are any differences in the clinical presentation and manifestations of COVID-19 symptoms within different age groups comparing Children (0-19), to Adults (20-64) and Older Adults (65+).

A common cause of death in COVID-19 patients other than respiratory illness causing direct lung damage and further infection with bacterial or viral pneumonia is thrombosis (clotting) and the development of pulmonary thromboembolism as reported by a study on the autopsy findings in COVID-19 patients with PCR confirmed testing (Elezkurtaj, S. *et al.*, 2021). The increased hypercoagulability may possibly be linked to the inflammatory response, the release of pro-inflammatory cytokines causing the various clinical manifestations of COVID-19. Clinical findings have also reported higher mortality rates in men, the elderly, and minorities (Black, Asian and minority ethnic groups, BAME, in the United Kingdom) (PHE, 2021). In the United States, in

comparison to White Non-Hispanic persons the mortality rates in minority groups are, American Indian or Alaska Native, Non-Hispanic persons (2.4 times higher mortality); Asian, Non-Hispanic persons (1.0 times higher mortality); Black or African American, Non-Hispanic persons (2.0 times higher mortality); Hispanic or Latino persons (2.3 times higher mortality) (CDC, 2021c).

There are several theories emerging behind the pathogenesis which predisposes some individuals more than others to more severe illness.

A study by Tai, W. *et al.* in 2020 identified that the receptor-binding domain of the SARS-CoV-2 spike protein binds to human Angiotensin-converting enzyme 2 (ACE2) receptor (a metalloproteinase) via the S1 subunit with higher affinity than that of SARS-CoV to enter cells in the human body. This highlights a potential mechanism behind the varying clinical presentation of symptoms in different individuals, being that tissues with cells expressing higher amounts of ACE2 receptor would have the means for higher entry of SARS-CoV-2 disrupting the balance of ACE/ACE2 and subsequently the Renin-Angiotensin-Aldosterone System (RAAS) (Tai, W. *et al.*, 2020).

RAAS as well as its role in maintaining blood pressure also has a key role in the inflammatory response. ACE converts Angiotensin I to Angiotensin II and the RAAS pro-inflammatory response is then initiated via Angiotensin II. Angiotensin II decreases Phosphatidylinositol 3-kinase (PI3Kinase), which leads to insulin resistance (Tai, W. *et al.*, 2020). This may be one proposed mechanism that would explain the new-onset cases of Diabetes reported in those who have had COVID-19 disease (Rubino, F. *et al.*, 2020). Angiotensin II also increases reduced nicotinamide-adenine-dinucleotide phosphate (NADPH) oxidase and subsequently results in Reactive Oxygen Species (ROS) activation via Nuclear Factor Kappa B (NFκB) phosphorylation increasing the production of proinflammatory factors such as Tumor Necrosis Factor-α (TNF-α), Tissue factor (TF), Plasminogen Activating Inhibitor-1 (PAI-1), and Monocyte Chemoattractant Protein-1 (MCP-1) (Dandona, P. *et al.* 2007).

A study by Hamming, I. *et al*. in 2004, on Coronavirus (SARS-CoV) determined that in the brain ACE2 surface protein was present only in the smooth muscle, the presence of ACE2 in the kidney was moderately positive in the parietal epithelia, weakly positive in the visceral glomerular epithelia, and abundantly positive in the brush border of the proximal tubular cells. In the gastrointestinal tract ACE2 was present in the brush border, the smooth muscle of the muscularis mucosae and muscularispropria, the enterocytes of all parts of the small intestines and absent in those of the colon despite being present in the endothelium of vessels from the colon, stomach and small intestine. In the lung ACE2 was notably present in the Type I and Type II alveolar epithelial cells, but only weakly present in the bronchial epithelial cells. Finally, it was notable that ACE2 was present in the endothelial cells of the larger arteries and veins in all tissues studied (Hamming, I. *et al.*, 2004). The findings of these studies provide a potential explanation for the varied clinical presentation of symptoms seen in different individuals ranging from Respiratory to Gastrointestinal and Cardiovascular symptoms of COVID-19.

More recently, there has been an emergence of cases of COVID-19 co-infection with influenza termed 'flu-rona', a study by Bai, L. *et al.* in 2021 on mice models pre-infected with influenza A found that it promoted a significantly increased infectivity of SARS-CoV-2, the study also found more severe lung-damage in these mice. One theory presented here is that influenza A has the ability to increase expression of ACE2 (Bai, L. *et al.*, 2021*).* This finding linked with the ACE2 proposed pathogenesis of COVID-19 infection may also provide another indicator as to why some individuals experience more severe infection than others.

A key question when looking at the clinical characteristics and manifestations of COVID-19 disease, and severity of illness is in examining what the predisposing factors are. The CDC after completing an evidence review process for each illness which increases the risk of developing severe COVID-19 infection determined the comprehensive list of illnesses supported by Meta-Analysis and/or by Systematic review to be: Cancer, Chronic Kidney Disease (CKD), Cerebrovascular Disease, COPD, Diabetes (both type I and type II), Heart Conditions (Heart Failure, Coronary Artery Disease, Cardiomyopathy), Smoking (present or past history), Obesity, Pregnancy (including recent history). Those conditions reported by the CDC to be supported by Case-Control, Cohort and Cross-sectional studies are: Down's Syndrome, HIV, neurological conditions such as Dementia, being Overweight, Chronic Lung Diseases (Interstitial Lung Disease, Cystic Fibrosis and Pulmonary Hypertension), Sickle Cell Disease, Organ or Blood Stem Cell transplant, Substance Use Disorders. The conditions reported by the CDC and supported by Case-Series and Case-Report studies are Asthma, Hypertension, Liver Disease and Immunodeficiencies. The CDC also reports that those aged 45 and above account for more than 95% of all COVID-19 deaths, and that those aged 65 and above account for more than 80% of all COVID-19 deaths and further reports that minorities tend to experience more severe symptoms at younger ages, as well as those with disabilities being at increased risk of COVID-19 infection due to a combination of being more likely to have a co-morbidity such as a chronic illness as well as experiencing

factors limiting access to adequate healthcare (CDC, 2021a). As such, it is important to consider what can be done in at-risk populations to both minimise risk of mortality and severity of illness.

The COVID-19 Alpha variant (B.1.1.7), was the strain that was first noted in the United Kingdom (September 2020), the Beta variant (B.1.351) was first observed in South Africa (May 2020), the Gamma variant (P.1) was the strain first identified in Brazil (November 2020) whilst the novel Delta variant (B.1.617.2) at present first identified in India (October 2020) has become the more dominant strain in circulation and displays a high transmissibility of COVID-19 (50% more transmissible than the Alpha variant for example) in particular amongst the unvaccinated population, and the early reports indicate that the symptoms are similar to other COVID-19 variants already in circulation within the population meaning there as yet have not been any clinical symptoms that may differentiate it from the original variants in circulation. The SARS-CoV-2 virus is continually mutating and at present there are two strains of concern and interest that have emerged, Lambda Variant (C.37) first identified in Peru (December 2020), and Mu variant (B.1.621) which was first identified in Colombia (January 2021), on top of these strains there are another 15 strains which emerged between March 2020 and January 2021 that are being monitored. The newest strain with higher transmissibility than the Delta variant is Omicron (B.1.1.529) which emerged in November 2021 and as of December 2021 has become the most dominant strain in circulation globally (WHO, 2021c).

Several long-term studies on long-COVID, have begun, with some presenting preliminary findings however it may be several years before sufficient data on this area has been collected and the full impact of the pandemic addressed. This makes the early identification of COVID-19 both through clinical presentation followed by regular testing important in taking early interventional measures to reduce the impact and prevent further spread of the illness throughout the local and global population.

A single centre study by Carfi, A. *et al.* in 2020 of 143 patients that were discharged from hospital following recovery from COVID-19 disease in Italy found that 12.6 % experienced no persistent symptoms, 32.2% had 1-2 persistent symptoms, whilst 55.2% experienced 3 or more persistent symptoms. Overall, 63% of patients reported a worsened quality of life, the predominate symptoms experienced in Long COVID were Fatigue in 53.1% of patients, followed by Dyspnea in 43.4%, Joint Pain 27.3%, Chest Pain in 21.7% of patients and it was found that that none of the patients reported symptoms of Fever or symptoms of acute illness with COVID-19 (Carfi, A., *et al.* 2020).

A similar study by Xiong, Q. *et al.* in 2021 of 538 patients 3 months after COVID-19 illness in Wuhan, China found that 49.6% reported experiencing General Symptoms, 39% experienced Respiratory Symptoms, 28.3% reported experiencing Fatigue or Physical Decline, with 23.6% experiencing Sweating, 22.7% experiencing Psychosocial symptoms, and Alopecia in 28%, it is notable 12.3% reported Chest Pain and 14.1% reported Chest Distress. Depression was found in 4.3% of patients, Anxiety in 6.5% and sleep disturbances in 17.7% (Xiong, Q. *et al.*, 2021).

The findings of the analysis of data from a Self-Reporting Symptom App by Sudre*et al.* in 2021 of individuals in the United States, United Kingdom and Sweden at both 28 days post COVID-19 (sample size 558 with confirmed PCR positive test) and at 56 days post COVID-19 (189 with confirmed PCR positive test) found that 97.7% and 96.8% reported Fatigue at 28 days and 56 days respectively, followed by Headache 91.3% (at 28 days) and 93.7% (at 56 days), Dyspnea reported in 70.8% (at 28 days) and 75.7% (at 56 days), Loss of Smell 72% (at 28 days) and 75.1% (at 56 days), Chest Pain 60%(at 28 days) and 63%(at 56 days), Skipped Meals, 59.5% (at 28 days) and 66.7% (at 56 days), Diarrhea 51.1% (at 28 days) and 54.5% (at 56 days), Abdominal Pain 44.1% (at 28 days) and 49.2% (at 56 days). Overall, the findings of this study determined that the main symptoms of Long COVID were Fatigue, Dyspnea, Headache and Loss of Smell (Sudre, C.H., *et al.*, 2021b). The differences in the findings of these three studies highlights that there is a wide range of Long COVID symptoms being experienced (See Table 4., Results section).

IV. Result:

The total number of Full-Text articles assessed for eligibility was 294. Of these, the number of relevant studies identified and selected for review was 48, 13 of which were then excluded as the symptoms of children and adults could not be separated which was a requirement for inclusion, leaving a total of 35 studies which were included in this investigation (See Figure 1. PRISMA Flow Diagram below, page 15).

The number of studies which provided data for Children (ages 0-19 years) was 24 and for the Adults (20-64) and Older Adults groups (65+) was 11. The total sample size for the Children's group from the 35 studies was 2,475, for the Adults group (20-64) it was 2,955 and for the Older Adults (65+) 3,561 from the 11 studies. The studies were a combination of retrospective cohort, case-series, two were cross-sectional and one was a prospective study.

The study locations were cross-continental, North America (United States; Texas, Chicago, and California), Europe (United Kingdom, Italy, Spain, and Turkey), Asia (Uzbekistan, Republic of Korea, Malaysia, Japan Middle East; Oman, China; Hong Kong Special Administrative Region, Shanghai, Wuhan,

Zhejiang province and Changsha), South America (Chile), and Africa (Nigeria). All background information on the 35 selected studies is provided in Table 1 below on page 16.

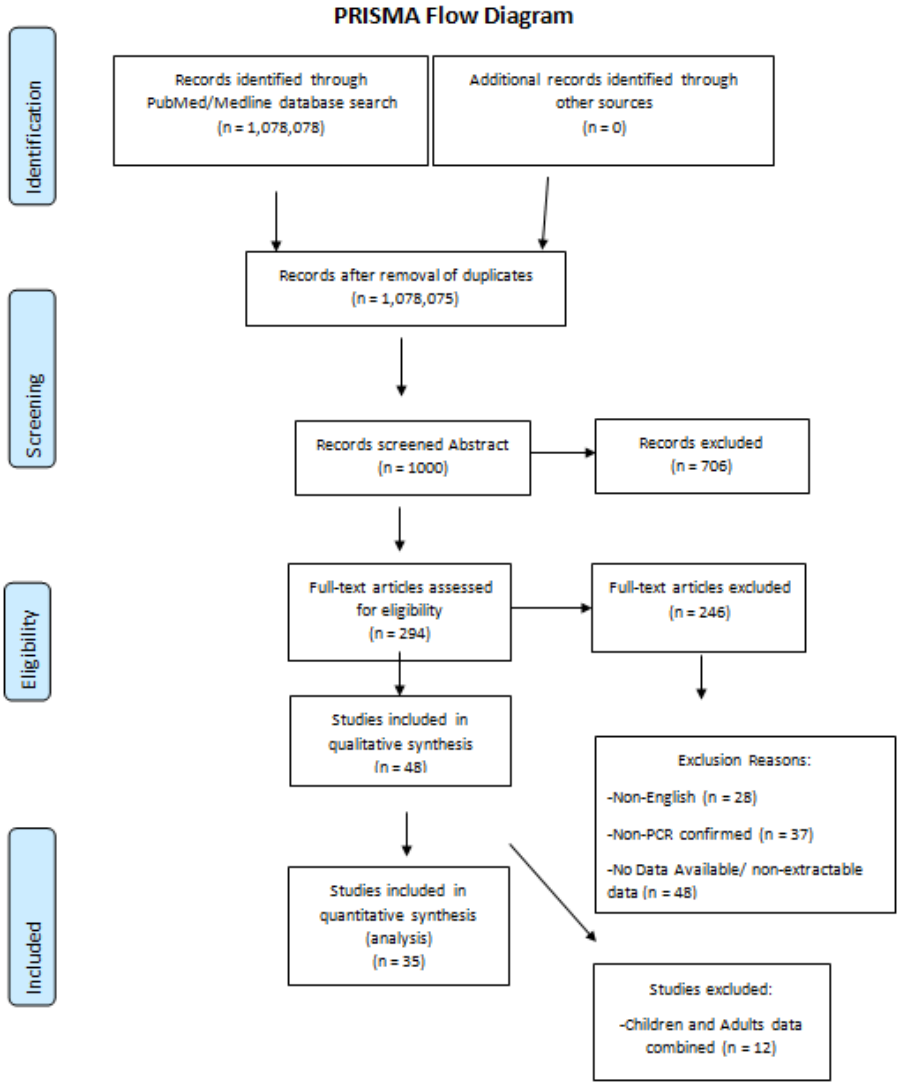

Figure 1. *PRISMA Flow Diagram, screening process for Systematic Review and Meta-Analysis. (Template Source: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71)*

Table 1: Information on the 35 studies selected for review

Children (n=2,475)	Author (Publication year)	Study Type	Location	Mean Age (Interquartile Range)	Sample Size
1	Adeji et al. (2020)	Cross-Sectional	Nigeria	12.63+/-4.31 years (1.5-18)	54
2	CDC (2020)	Case Series	United States		291
3	Chua et al. (2020)	Cohort	Korea, Hong Kong Special Administrative Region (HKSAR) and Wuhan	0 to 17	423
4	De Jacobis et al. (2021)	Retrospective Cohort	Italy	1 to 18	66
5	Du et al. (2020)	Retrospective	China	6 (3 days to 15 years)	182
6	Foster et al. (2020)	Retrospective	United States, Texas	0.1 to 20.2	57
7	Garazzino et al. (2020)	Multi-centre	Italy	5 (1 day to 17 years)	168
8	Garcia et al. (2020)	Multi-centre prospective	Spain	0 to 18	74
9	Han et al. (2021)	Case Series	Republic of Korea	0 to 18	91
10	Kanthimathinathanet	Retrospective Case-	United Kingdom	3.5 (0 to 12)	45

	al. (2020)	Series			
11	Kim et al. (2020)	Retrospective	Uzbekistan	0-17	46
12	Korkmaz et al. (2020)	Observational Cohort	Turkey	9.5 median (3.16-15.08)	81
13	Leung et al. (2020)	Comparative Retrospective	China	9 hours to 17 years	43
14	Mannheim et al. (2020)	Case Series	Illinois, Chicago, United States	0-17	64
15	Ng et al. (2021)	multi-centre, retrospective observational	Malaysia	6 (3 to 10)	261
16	Parri et al. (2020)	Case Series Descriptive	Italy	0-17	130
17	Peng et al. (2020)	Retrospective	Wuhan, China	0-15	75
18	Qui et al. (2020)	Observational Cohort	China	0-16	36
19	Wang et al. (2020)	Retrospective	Northern China	6 months-17 years	31
20	Xia et al. (2020)	Retrospective	Wuhan, China	1 day to 14 years 7 months,median 2 years and 1.5 months	20
21	Yao-Ling et al. (2020)	Retrospective	Wuhan, China	under 18	115
22	Yazidi et al. (2021)	Retrospective	Oman, Middle East	0-14	56
23	Zhang et al. (2020)	Retrospective	Italy	0-14	41
24	Zheng et al. (2020)	Cross-Sectional multicenter Retrospective	Hubei, China	3 months-14 years	25
Adults (N=6516)	**Author**	**Study Type**	**Location**	**Mean Age (Interquartile Range)**	**Sample Size**
25	Brill et al. (2020)	Retrospective Cohort	United Kingdom	72 (56, 83 IQR)	450
26	Chen et al. (2020)	Retrospective, Single Center	Shanghai, China	51(36–64)	249
27	Duanmu et al. (2020)	observational, cross-sectional	Northern California, United States	45 [32–65]	100
28	Mallah et al. (2021)	Retrospective clinical and population-based analysis	Middle East (Multinational Cohort)	46.2 +- 16	1792
29	Morikawa et al. (2021)	Retrospective	Tokyo, Japan	Mean 44 (32-56)	154
30	Ramos et al. (2021)	Retrospective, Observational study, Multicenter	Spain	86.3 (83.2-89.6)	2772
31	Wang et al. (2020)	Wuhan, China	Wuhan, China	69 (65-76)	339
32	Xie et al. (2020)	Retrospective Observational	China	56.5 (49.25-64.75)	56
33	Xu et al. (2020)	Retrospective Case-Series	Zhejiang province, China	32-52	62
34	Vial et al. (2020)	Retrospective	Santiago, Chile	39 (28–65)	381
35	Zheng et al. (2020)	Retrospective	Changsha, Hunan, China	Mean 45 (33.5 to 57)	161

Table 1. *Information on 35 studies selected for review, 24 studies provided data for the Children's (0-19) group and 11 studies provided data for the Adults (20-64) and Older Adults (65+) groups*

Findings on the Clinical Presentation and Characteristics of COVID-19 for each age group, Children (0-19), Adults (20-64) and Older Adults (65+)

Children (0-19)

The most common reported symptoms were Fever (46.9%), Refusal to eat/Anorexia (45%), Dry Cough (39%) in comparison to Productive Cough (15.6%), Unspecified Respiratory (36.9%), Unspecified Gastrointestinal (20.9%), Respiratory distress (19.6%), Irritability (16.1%), followed by Nasal Congestion/Rhinorrhoea (15.6), Fatigue/Lethargy (15.2%), Headache and ARDs both reported 14.9%, Sneezing (14.8%) and Diarrhea (11%), and Nausea/ Vomiting (8%), the lowest reported symptoms were Anosmia (2.4%), Ageusia (3.9%), Chills (5.2%), Myalgia and Arthralgia (6%) and Chest Pain/ Discomfort (3%). Overall, the

studies focused on children reported more symptoms than those reported in adults (see Table 2), note: 37.6% of participants were asymptomatic.

Adults (20-64)

The most common reported symptoms were Cough (Dry 48.8%), followed by Chills (47.4%), Fever (42.2%), Fatigue/Lethargy (33%), Sore Throat/Pharyngitis (26.1%), Dyspnea (16.7%), Myalgia/ Arthralgia (16.4%), Headache (10.9%), with less commonly reported symptoms being Nasal Congestion/ Rhinorrhea (9.5%), Chest Pain/ Discomfort (9.1%), Diarrhea (6.2%), with loss of taste and loss of smell both at 5.6% and Anorexia/ Refusal to eat (3.2%). The remaining symptoms which were reported in Children but not in the studies for Adults were not reported which may mean either study participants did not experience these symptoms or if present they were not reported, subsequently no conclusion can be drawn from this study on the unreported symptoms (See Table 2).

Older Adults (65+)

The most common reported symptoms in this subgroup were Fever (72.6%), Cough (61.5%) compared to Productive Cough/ Expectoration (27.4%), Dyspnea (59.7%), Fatigue/Lethargy (37.3%), Confusion (29.4%), Chest pain/Discomfort (26%), Anorexia/ Refusal to eat (22.6%), Diarrhea (14.3%) with less common symptoms reported Nausea/ Vomiting (5.2%), Myalgia/Arthralgia (4.7%), Dizziness (3.8%) and Headache (3.5%). Similarly, to the Adults group (20-64), the remaining symptoms that were present in the Children's group were not reported in the Older Adults (65+) group, which may mean they were not experienced by patients or that the data was not reported. As such conclusions on the remaining symptoms cannot be drawn from this study (See Table 2).

Table 2: Frequency of Clinical Symptoms of COVID-19 reported for each age group, Children (0-19), Adults (20-64) and Older Adults (65+)

Clinical Symptoms of COVID-19	Frequency (%) Children 0-19 (n = 2,475)	Frequency (%) Adults 20-64 (n = 2,955)	Frequency (%) Older Adults 65+ (n = 3,561)	Frequency (%) All Adults (n =6,516)
Abdominal Pain	6.1 (n = 43/ 705)	-	-	-
Anorexia/ Refusal to eat	45 (n = 54/ 120)	3.2 (n = 8/ 249)	22.6 (n = 702/ 3111)	21.1 (n = 710/ 3360)
Ageusia (Loss of taste)	3.9 (n = 22/ 570)	5.6 (n = 109/ 1946)	-	5.6 (n = 109/ 1946)
Anosmia (Loss of Smell)	2.4 (n = 17/ 705)	5.4 (n = 105/ 1946)	-	5.4 (n = 105/ 1946)
ARDS	14.9 (n = 11/ 74)	-	-	-
Asymptomatic	37.6 (n = 354/ 942)	2.8 (n = 7/ 249)	-	2.8 (n = 7/ 249)
Chest Pain/ Discomfort	3 (n = 13/ 434)	9.1 (n = 213/ 2329)	26 (n = 88/ 339)	11.1 (n = 301/2668)
Chills	5.2 (n = 8/ 155)	47.4 (n = 754/ 156)	-	.47.4 (n = 754/ 156))
Confusion	-	-	29.4 (n = 815/ 2772)	29.4 (n = 815/ 2772)
Cough (Dry)	39 (n = 808/ 2069)	48.8 (n = 1442/ 2955)	61.5 (n = 2190/ 3561)	54.6 (n = 3315/ 6066)
Cough (Productive/ Expectoration)	15.6 (n = 112/ 719)	-	27.4 (n = 93/ 339)	27.4 (n = 93/ 339)
Diarrhoea	11 (n = 185/ 1679)	6.2 (n = 151/ 2420)	14.3 (n = 509/ 3561)	10.1 (n = 560/ 5531)
Dizziness	1.1 (n = 5/ 469)	-	3.8 (n = 13/ 339)	3.8 (n = 13/ 339)
Dyspnoea	9.5 (n = 66/ 694)	16.7 (n = 475/ 2837)	59.7 (n = 2125/ 3561)	40.3 (n = 2580/6398)
Fever	46.9 (n = 1024/ 2184)	42.2 (n = 1247/ 2955)	72.6 (n = 573/ 789)	47.3 (n = 1558/3294)
Fatigue/ Lethargy	15.2 (n = 100/ 658)	33 (n = 384/ 1163)	37.3 (n = 1161/ 3111)	36.1 (n = 1545/ 4274)
Headache	14.9 (n = 88/ 589)	10.9 (n = 148/ 1355)	3.5 (n = 12/ 339)	15 (n= 160/ 1065)
Irritability	16.1 (n = 18/ 128)	-	-	-
Myalgia/ Arthralgia	6 (n = 57/956)	16.4 9 (n = 372/ 2263)	4.7 (n = 16/ 339)	14.9 (n = 388/ 2602)
Nasal Congestion/ Rhinorrhoea	16.9 (n = 2257/1525)	9.5 (n = 33/ 349)	-	9.5 (n = 33/ 349)
Respiratory Distress	19.6 (n = 40/ 204)	-	-	-
Seizures/ Convulsions	3.9 (n = 18/ 465)	-	-	-
Sneezing	14.8 (n = 8/ 54)	-	-	-
Sore Throat/ Pharyngitis/ Odynophagia	9.6 (n = 108/ 1120)	26.1 (n = 205/ 786)	3.8 (n = 13/ 339)	9.4 (n = 368/ 3897)
Nausea/ Vomiting	8.2 (n = 125/ 1532)	5.6 (n = 114/ 2053)	5.2 (n = 163/ 3111)	5.3 (n = 368/ 2392)
Cardiovascular Unspecified	8.9 (n = 4/ 45)	-	-	-
Gastrointestinal Unspecified	20.9 (n = 88/ 421)	-	-	-
Respiratory Unspecified	36.9 (n = 93/ 252)	-	-	-
Renal Unspecified	6.7 (n = 3/ 45)	-	-	-
Neurological Unspecified	8.9 (n = 9/ 101)	-	-	-

Table 2: *Frequency of Clinical Symptoms of COVID-19 disease reported for each age group, Children (0-19), Adults (20-64) and Older Adults (65+), boxes with a (-) symbol indicate that there was no data reported for that symptom in the results section or data tables and figures provided by the studies used.*

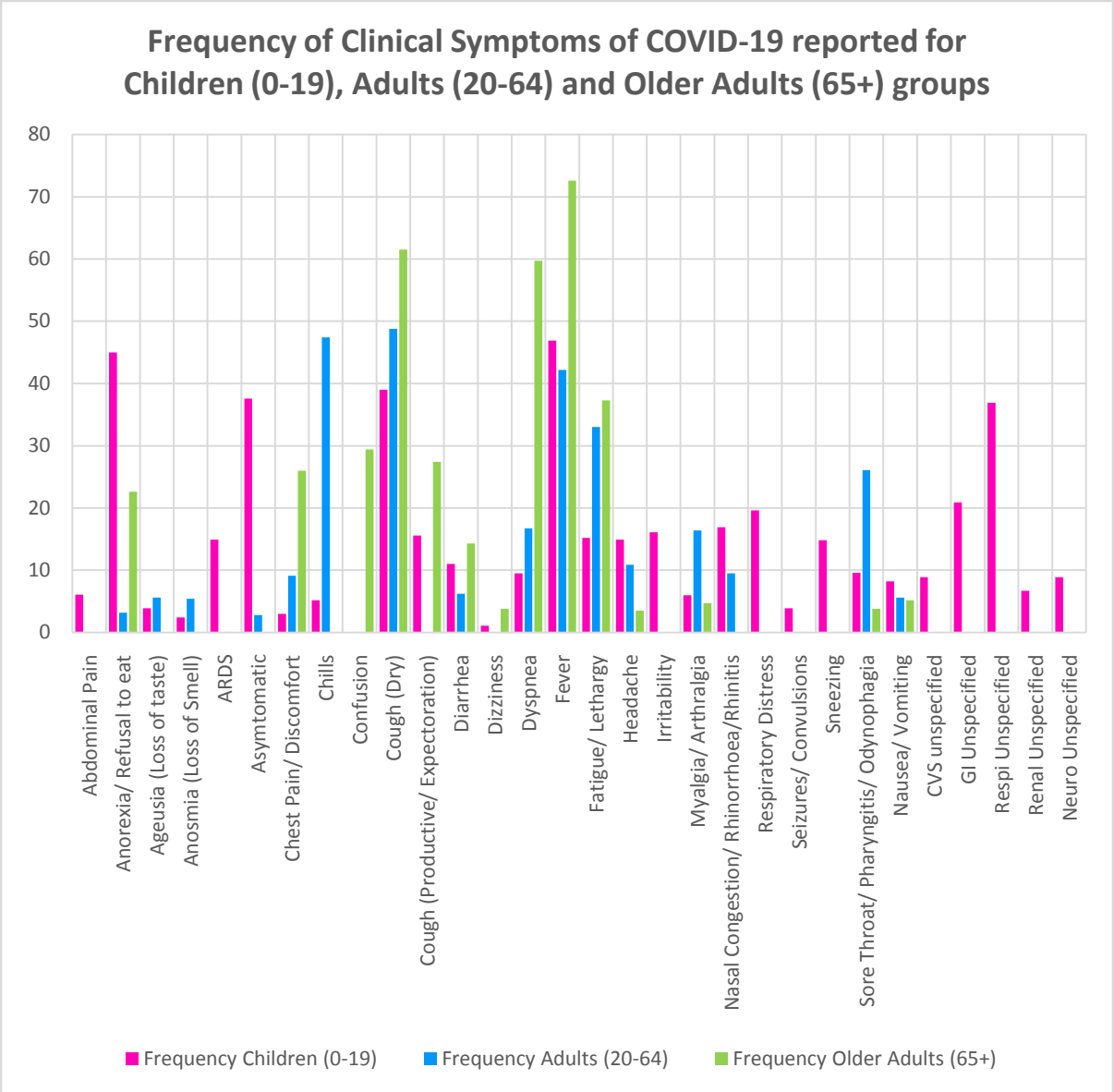

Figure 2. *Graph of the Frequency of Clinical Symptoms reported for each age group comparing Children (0-19) to Adults (20-64) and Older Adults (65+).*

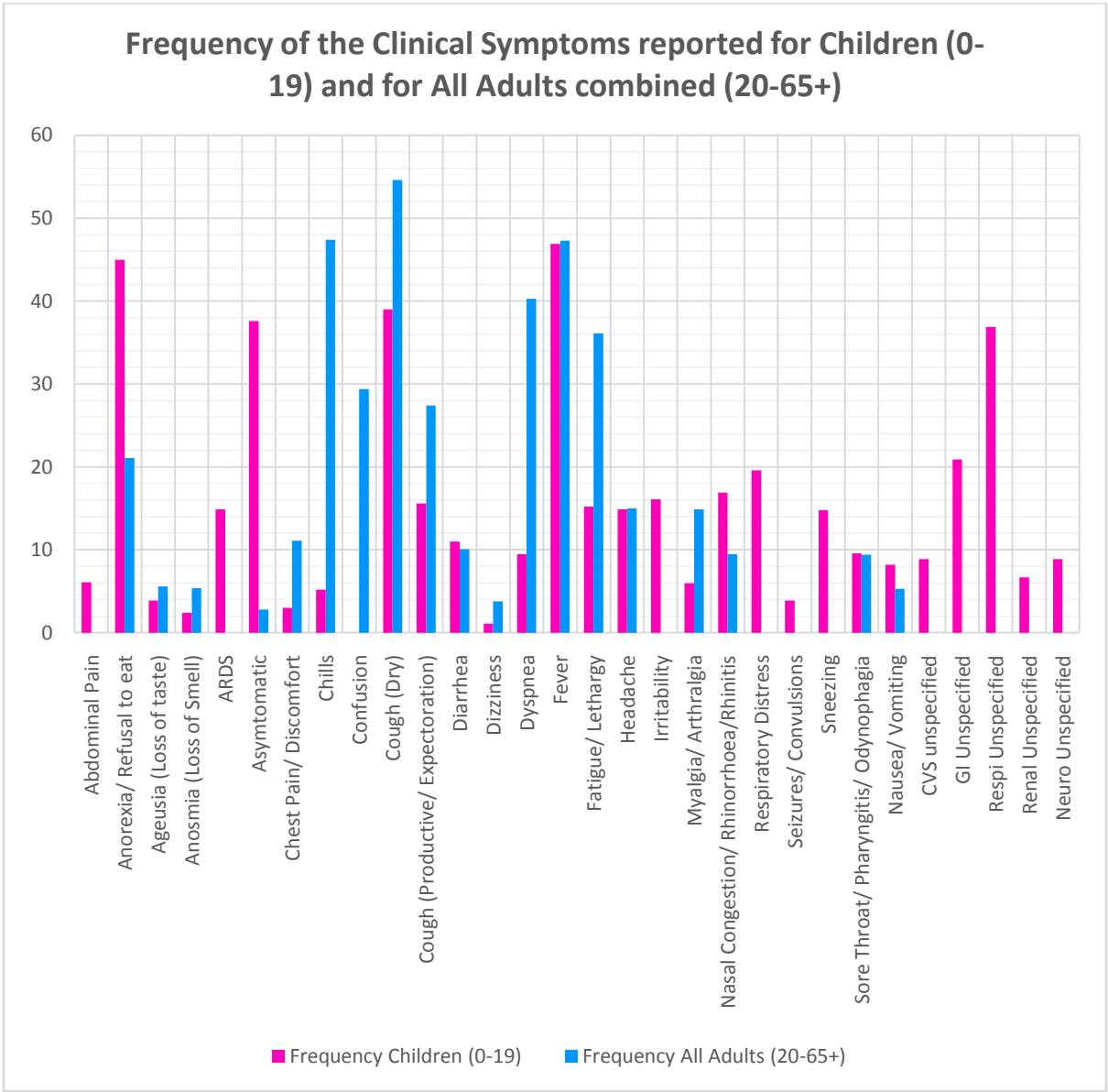

Figure 3. *Graph of the Frequency of Clinical Symptoms of COVID-19 disease reported for the Children's (0-19) group compared to All Adults combined group (20-65+).*

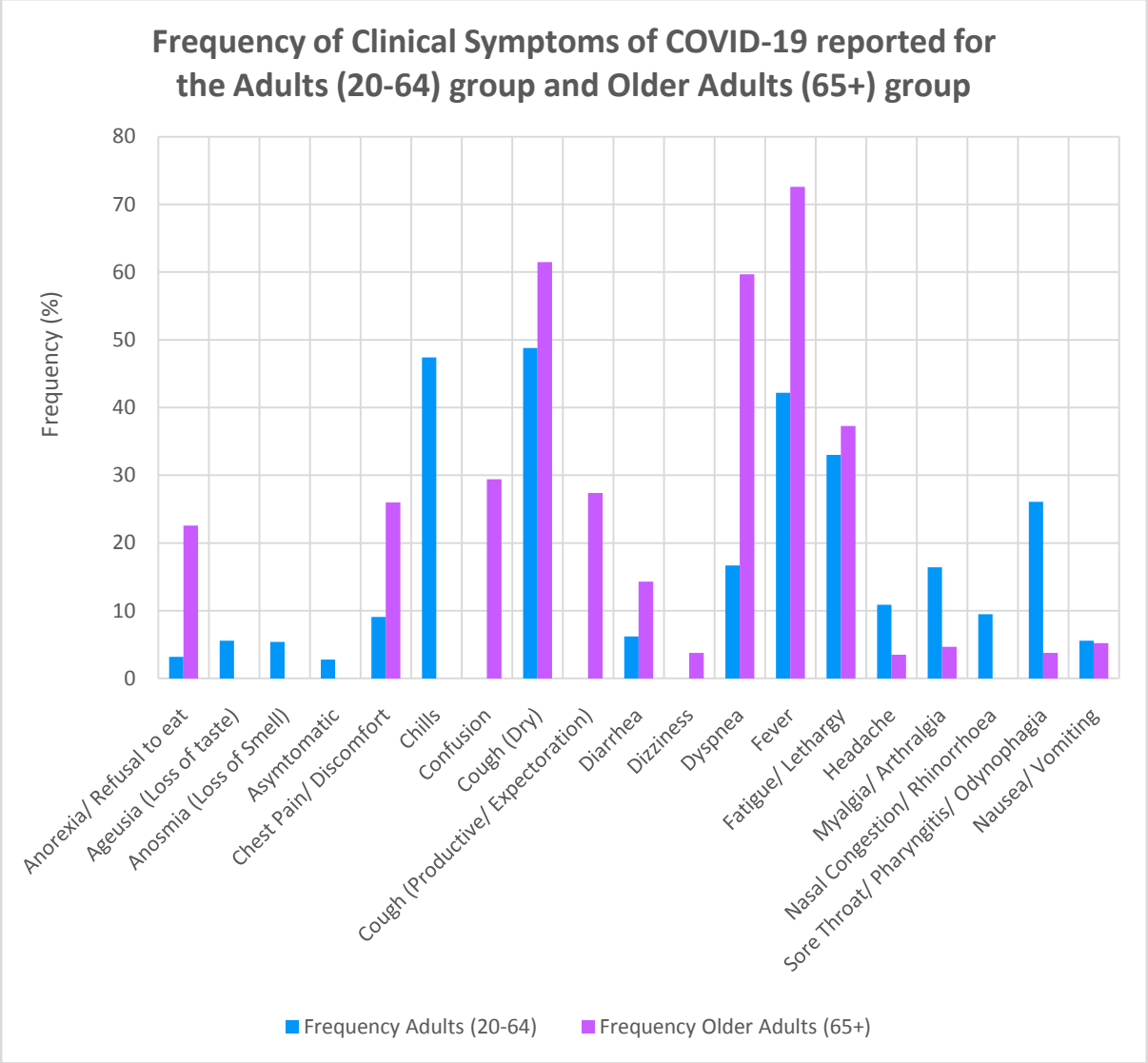

Figure 4. *Frequency of Clinical Symptoms of COVID-19 disease reported for the Adults (20-64) group compared to the Older Adults (65+) group.*

Table 3: The Top 5 Most Common Reported Clinical Symptom of COVID-19 disease for each age group

Most Common Symptom	Children (0-19)	Adults (20-64)	Older Adults (65+)
1	Cough	Cough (dry)	Cough
2	Fever	Chills	Fever
3	Refusal to eat/ anorexia	Fever	Dyspnea (Shortness of breath)
4	Unspecified Respiratory	Fatigue/Lethargy	Fatigue/Lethargy
5	Unspecified Gastrointestinal	Sore Throat	Confusion

Table 3. *The Top 5 most common reported Clinical Symptoms in the children and adolescents (0-19) group, Adults (20-64) group, and the Older Adults (65+) age groups.*

The findings presented in ***Figure 2.*** *Graph of the Frequency of Clinical Symptoms reported for each age group comparing Children (0-19) to Adults (20-64) and Older Adults (65+)* are thatCough was the most common symptom followed by Fever which was considerably higher in Older Adults than in Adults and Children, and only marginally higher in Children than in Adults. Dyspnea in Older Adults was the 3rd most common symptom compared to Anorexia/Refusal to Eat being the 3rd most common in Children.

The findings presented in ***Figure 3.*** *Graph of the Frequency of Clinical Symptoms of COVID-19 disease reported for the Children's (0-19) group compared to All Adults combined group (20-65+)* are that the Children's group shows a wider spread of reported clinical presentation with the Gastrointestinal symptom of

Anorexia/Refusal to Eat (45%) being markedly higher than in Adults (3.2%). When Older Adults and Adults are combined Fever is comparable to that in Children which differs from when Adults and Older Adults are separated.

The findings presented in ***Figure 4.*** *Frequency of Clinical Symptoms of COVID-19 disease reported for the Adults (20-64) group compared to the Older Adults (65+) group* are thatFever was the 2nd most common symptom for Older Adults after Cough and considerably higher than in Older Adults. Chills was the 2nd common symptom in Adults, and Dyspnea was the 3rd most common symptom in Older Adults. Severe symptoms as classified by the World Health Organization such as Chest Pain and Confusion were also more frequently reported in Older Adults compared to in Adults.

And the findings presented in ***Table 3.*** *The Top 5 most common reported Clinical Symptoms in the children and adolescents (0-19) group, Adults (20-64) group, and the Older Adults (65+) age groups* are thatfor all age groups Cough was the most common symptom followed by Fever in Children and Older Adults, and Chills in Adults. Refusal to eat/ anorexia was the 3rd most common symptom in Children, Fever for Adults was the 3rd most common symptom and Dyspnea for Older Adults was the 3rd most common symptom. Severe symptoms as described by WHO being Dyspnea, Confusion and Chest Pain/ Discomfort (6th most common symptom in Older Adults) were the top symptoms seen in Older Adults but not in the Children or Adults Groups.

Table 4: Symptoms of Long COVID following recovery from COVID-19 disease reported by Organ System

	Study 1	Study 2	Study 3
Author (Year)	Carfi, A.*et al.* (2020)	Xiong, Q.*et al*. (2020)	Sudre, C.H.*et al*. (2021b)
Location	Italy	Wuhan, China	Sweden, United Kingdom and United States
Time post COVID-19	>3 months	> 3 months	28 days (28D) and 56 days (56D)
Sample Size	143	538	558 (28D), 189 (56D)
Age	Mean 56.5 (SD 14.6), 18-84 Years	Median IQ Range 52 41-62 Years	Mean 48.9 (12.7); (28D), 50.9 (12.5); (56D)
Long-Covid Symptoms by System:			
General	Fatigue (53.1%)	Fatigue/Physical decline (28.3%) Sweating (23.6%) Chills (4.6%) Discontinuous flushing (4.8%)	Fatigue (97.7%, 28D; 96.8% 56D) Fever (62.9%, 28D; 58.7%, 56D)
Skin	-	Alopecia (28.6%)	-
HEENT	-	Sore throat (3.2%)	Headache (91.3%,28D; 93.7% 56D) Loss of Smell (72%, 28D; 75.1%, 56D) Sore throat (67%, 28D; 72.5%, 56D)
Respiratory	Dyspnea (43.4%)	Post Activity Polypnea (21.4%) Non-Motor Polypnea (4.7%) Cough (7.1%) Sputum (3%)	Dyspnea (70.8%, 28D; 75.7%, 56D) Persistent Cough (68.6%, 28D; 62.4%, 56D)
Cardiovascular	Chest Pain (21.7%)	Chest distress (14.1%) Chest pain (12.3%) Limb edema (2.6%) Increased resting heart rate (11.2%) New hypertension (1.3%)	Chest Pain (60%, 28D; 63%, 56D)
Gastrointestinal	-	-	Loss of appetite/ missed meals (59.5%, 28D; 66.7%, 56D) Diarrhea 51.1%, 28D; 54.5%, 56D) Abdominal Pain (44.1%, 28D, 49.2%, 56D)
Urinary	-	-	-
Musculoskeletal	Arthralgia (27.3%)	Arthralgia 7.6% Myalgia 4.5%	-
Neurologic/ Psychiatric/ Behavioural	Worsened Quality of Life (63%)	Dizziness (2.6%) Somnipathy (17.7%) Depression (4.3%) Anxiety (6.5%) Dysphoria (1.7%) Feeling of inferiority (0.6%)	Delirium (30.3%, 28D; 38.6% 56D)

Table 4. *Long COVID Symptoms data reported by Organ System from Study 1. Carfi, A. et al. (2020), Study 2. Xiong, Q. et al.(2020) and Study 3. Sudre, C.H. et al. (2021b), (see Literature Review, Chapter III).*
The findings from the Literature Review, Chapter III on the symptoms of Long COVID are reported in **Table 4**. Long COVID symptoms in each study were those reported after recovery from PCR positive confirmed cases of COVID-19 disease. This was after 3 or more months in Study 1 and Study 2, and after both 28 days and 56 days in Study 3. The findings highlight that multiple organ systems appear to be affected in Long-Covid at varying rates from General, HEENT, Skin, Cardiovascular, Gastrointestinal, Respiratory, Musculoskeletal and Neurological/ Psychiatric. It was notable that no Renal symptoms were reported. Fatigue, Shortness of Breath and Chest Pain were the most commonly reported symptoms across all three studies. Sore Throat, Cough, Myalgia/Arthralgia were reported in two of the three studies, whereas Headache, Loss of Smell, Abdominal Pain, Diarrhea, Loss of Appetite, Dizziness, Somnipathy, Anxiety, Depression, Deliurm and Alopecia were each reported in only one of the three studies.

Data Analysis by Clinical Symptom of COVID-19 disease reported for Children aged 0-19 (C), Adults aged 20-64 (A) and Older Adults 65+ (OA) groups.

Cough for all groups was the most common reported symptom when Dry Cough (Children, C: 39%, Adults, A: 48.8%, Older Adults, OA 61.5%) and Productive Cough/ Expectoration (C: 15.6%, A: N/A, OA: 27.4%) figures are combined. The prevalence in the Older Adults group was the highest, and the lowest in the Children's group.

Fever was the second most reported symptom in both the Older Adults (OA) group and in the Children's (C) group. Fever in the OA group (72.6%) was found to be 1.55 times higher than in the Children's (46.9%) and 1.49 times higher than in the Adults group (42.2%) where it was the 3rd most common symptom after **Chills** (47.4%); Chillswere 9.1 times higher in Adults than in Children (5.2%), no data for Chills was available for comparison with the Older Adults group.

Dyspnea (shortness of breath) was the 3rd most common symptom in the Older Adults group (59.7%) which was 6.28 times higher than in the Children's group (9.5%) and 3.57 times higher than in the Adults group (16.7%).

Refusal to eat/ Anorexia was the 3rd most common symptom in Children (45%) and was found to be and 14 times higher than in Adults (3.2%) compared to being only 1.99 times higher in Children than in Older Adults where it was the 8th most common symptom (22.6%).

Fatigue/Lethargy was the 4th most common symptom in both the Older Adults (37.3%) and Adults (33%) groups. Older Adults was found to be 2.45 times higher than in Children (15.2%) and the Adults was 2.17 times higher than in Children.

Confusion was the 5th most common reported symptom in Older Adults (29.4%), no comparable data was available for the Children, and Adults groups.This was followed by **Chest pain and Discomfort** (26%) being the 6th most common symptom in Older Adults which was 8.67 times more common than in Children (3%) and 2.86 times more common than in Adults (9.1%).

Sore throat/ Pharyngitis/ Odynophagia was the 5th most common reported symptom in Adults (26.1%) which was 6.87 times higher in Older Adults (3.8%) and 2.72 times higher than in the Children's group (9.6%).

Respiratory Distress and ARDs were reported in the Children's group and were 19.6% and 14.9% respectively, and Unspecified Respiratory was 36.9% which was the 5th most common reported symptom Children after **Asymptomatic** (37.6%). None of these findings were reported in the Adults group and the Older Adults group for comparison, except for Asymptomatic (2.8%) in the Adults group. However, the findings of asymptomatic patients in the studies used would not be reflective of the findings in the general population as the participants of the studies used were selected via hospital records and positive PCR-Test in both inpatient and outpatient settings. Patients admitted to hospital with COVID-19 would predominantly be expected to be symptomatic over being asymptomatic.
Diarrhea in Older Adults was the 9th most common reported symptom (14.3%) which was 2.3 times more common than in Adults (6.2%) and 1.3 times more common than in Children (11%).

Nausea and Vomiting in Children (8.2%) was 1.46 times higher than in Adults (5.6%) and 1.58 times higher than in Older Adults (5.2%).

Loss of taste (Ageusia) and Loss of Smell (Anosmia) were both higher in the Adults group than in Children, there was no available date for the Older Adults group for comparison. Ageusia was 1.44 times higher in Adults (5.6%) than Children (3.9%), and Anosmia was 2.25 times higher in Adults (5.4%) than in Children (2.4%).

V. Discussion

There were a number of limitations in this study, 1. Only studies available in English were selected for evaluation, 2. Due to the use of secondary data in this study and limited access to the raw original data, only data that could be extracted from the results sections, data tables and figures provided by the selected studies could be used, studies which met the eligibility criteria but had combined the data for all ages of patients with no way to extract data for each age group were excluded. 3. Of the 35 selected studies although the sample sizes for each age group were similar and well sized for evaluation (C: 2,475, A: 2955 and OA: 3,561) not every study reported values for each symptom, this may have either been due to study participants not having reported experiencing a symptom in which case the value to be included in this evaluation would have been 0, or the figure may not have been significant enough for the studies used to include in their published data results section, which meant that for this study there was no data available for that symptom to be reported on and included, those are marked as (-) no data available in the results section of this study and were not used in the evaluation, only reported figures of 0 were included.

It is also notable that the Omicron variant (B.1.1.529) despite its increased transmissibility has been found to affect the lungs less than its predecessor variants of concern such as the Delta variant which too has high transmissibility. The data set evaluated in this study pre-dates the emergence of the Omicron variant and the first detection of the Omicron variant globally in November 2021, meaning the findings of this study to determine if there are any differences in the clinical presentation of COVID-19 in Children, Adults and Older Adults can be attributed to the pre-Omicron variants of SARS-CoV-2 in circulation at the time in 2019 to early 2021. The findings of this study also predate the distribution of COVID-19 vaccines so all individuals evaluated were unvaccinated at the time of their COVID-19 infection and clinical presentation of symptoms.

The data set presented a wider range of clinical symptoms reported in the Children's (0-19) group than for both the Adults (20-64) and Older Adults (65+) groups. Unreported symptoms in the Adults and Older Adults groups that were reported in the Children's group could not be compared as it was unclear whether these values were not reported because they were not experienced by study participants (0%) or just not reported in the studies data set which was one limitation of this study. It is notable that for the Children's group 20.9% of symptoms were Unspecified Gastrointestinal and Unspecified Respiratory 36.9% which means that the individual symptoms reported for children for respiratory and gastrointestinal may in fact be higher than the reported figures.

The top 5 symptoms for Children were Cough (combined dry and productive), Fever, Anorexia/ refusal to eat, Unspecified Respiratory and Unspecified Gastrointestinal symptoms. The top 5 symptoms for Adults (20-64) were Cough (dry), Chills, Fever, Fatigue/ Lethargy and Sore Throat. And for the Older Adults group (65+) the top 5 symptoms were Cough (dry and productive combined), Fever, Dyspnea and Fatigue/ Lethargy and Confusion as reported in Table 3. The information on COVID-19 symptoms provided to the global public by the World Health Organization (WHO), lists the most common symptoms as being, Fever, Cough, Tiredness, and Loss of Taste/ Loss of Smell. The less common symptoms are listed as being Sore Throat, Headache, Aches and Pains, Diarrhea, Rash on skin/ finger/ toe discolouration and Red/ Irritated eyes. And the most serious symptoms as being Shortness of Breath/Difficulty Breathing and Loss of Speech, Mobility, or Confusion. The findings of this study indicate that for Adults (20-64) Sore Throat was the 5th most common symptom, for Children after Cough and Fever, Refusal to eat/ Anorexia was the 3rd most common reported symptom with Unspecified Respiratory and Unspecified Gastrointestinal being the 4th and 5th most common reported symptoms, the severe symptoms listed by WHO, Dyspnea (shortness of breath) for example was more frequently reported in the Older Adults (65+) as the 3rd most common symptom, and Confusion as the 5th most common reported symptom. Fatigue and lethargy was the 4th most common symptom in Adults (20-64) and Older Adults (65+) age groups but not in the top 5 for Children. Loss of Taste and Smell for all age groups was found to be one the least common symptoms, but when present was higher in the Adults (20-64) age group than for Children (0-19) and Older Adults (65+). The findings in this study do echo some of the findings of theSudre C.H., *et al.* 2021(a) King's College London, Massachusetts General Hospital study with the ZOE Symptom app as discussed in the Literature Review section. Children (0-19) in comparison to Adults (20-64) and the Older Adults (65+) have more gastrointestinal symptoms with Refusal to eat/ Anorexia being the 3rd most common symptom for this age group. Chills was found to be more common in Adults (20-64) than in Children and Adolescents, and Fever for all age groups was in the top 2-3 most common symptoms, with Cough as the number 1 most common clinical symptom across all age groups. The Sudre, C.H. *et al.* 2021(a) study also indicated that the symptoms of Loss of Taste and Smell, which although were less frequently reported in this study, had a greater correlation with a positive COVID-19 test which may serve as an important indicator for positive COVID-19 infection.

The findings of the Literature Review, Chapter III also revealed several interesting answers to the research of objectives of this study. The first being that one of the reasons that some individuals develop more severe illness than others as reported by the CDC is due to age, with more than 80% of deaths due to COVID-19 infection being in adults aged 65+, and 95% of deaths occurring in adults aged 45 and above (CDC, 2021a). What was notable about the frequency of symptoms experienced by patients in this study which correlates to the CDC reporting was that the older adults age group (65+) experienced symptoms that were classified by WHO as severe symptoms (life-threatening) these were Dyspnea as well as Confusion which were both in the top 5 symptoms of those aged over 65 and not in the top 5 symptoms experienced by the Adults and Children's age groups.

A second reason that some individuals experience more severe symptoms than others was due to comorbidities as well as long-standing social and systemic health inequalities which in particular have been reported to affect minorities with the CDC reporting that they are more susceptible to higher mortality rates at younger ages, similarly individuals with disabilities that are more likely to also have other comorbidities such as chronic health conditions combined with experiencing barriers to accessing adequate healthcare. On a more global scale, the barriers to healthcare become even more prominent when looking at the comparison between developing and more developed countries. The factors which are to be considered are a combination of the social, physical, and economic environmental determinants of health (WHO, 2017). Globally, for example, non-communicable diseases (NCD's, also known as chronic diseases) account for 71% of all deaths (41 million deaths annually). The top four NCDs in order being Cardiovascular Disease (CVD, 17.9 million annual deaths), Cancer (9.3 million annual deaths), Respiratory Diseases (4.1 million annual deaths) and Diabetes (1.5 million annual deaths), which are all some of the aforementioned co-morbidities associated with the increased risk of development of severe COVID-19 infection. These NDC's also affect individuals from low to middle income countries more predominantly than those in higher-income countries (WHO, 2018).

The Literature Review also provided insight into the emerging theories on the pathogenesis of COVID-19, such as the identification of the receptor-binding domain of the novel SARS-CoV-2 spike protein which has been found to bind to the ACE2 receptor via the S1 subunit with higher affinity than that of SARS-CoV to enter cells in the human body and potentially disrupt the ACE/ACE2 balance by Tai, W. *et al.* in 2020. The implications of this knowing the role of RAAS on regulating blood pressure but also in particular is the role of increased Angiotensin II in the proinflammatory response, as well as in the development of insulin resistance by Dandona, P. *et al.* 2007, may be one mechanism behind the reports of new onset cases of Diabetes reported in COVID-19 patients (Rubino, F. *et al.*, 2020) and new onset Hypertension reported in the Xiong, Q. *et al.* 2020 study (see Table 4.).

Furthermore, the findings of the presence of the ACE2 receptor in multiple tissues, in different organ systems from the Respiratory system (ACE2 presence on Type I and Type II alveolar epithelial cells in the lung), to the Gastrointestinal system (ACE2 presence in all enterocytes of the small intestines despite absence in the colon, and presence in the smooth muscle of the muscularispropria and muscularis mucosae) and the Cardiovascular system (ACE2 present in the endothelial smooth muscle of the large arteries and veins of all tissues sampled) in different individuals by Hamming, *et al.*, 2004. Along with the more recent findings of co-infection with influenza A which was found to increases the expression of ACE2 leading to more severe illness in mice models found by Bai, L. *et al.* in 2021 overall also provides a potential explanation for the varied clinical symptoms and manifestations. Similarly, the studies on the symptoms Long-Covid reported in Table 4. Also highlight that multiple organ systems appear to be affected following COVID-19 disease recovery most notably were the Cardiovascular (Chest Pain and Discomfort, new onset hypertension), Gastrointestinal (Abdominal Pain, Diarrhea, Loss of Appetite), Respiratory (Dyspnea, Cough), HEENT (Loss of Smell and Sore Throat) and Neurologic/Psychiatric (Somnipathy, Anxiety, Depression and worsened quality of life) and General which includes symptoms of Fatigue which was the most commonly reported symptom of Long-Covid across all three studies.

VI. Summary and Conclusion

In conclusion, the main purpose of this study was to aggregate data on PCR confirmed cases of SARS-CoV-2 infection to clearly identify the clinical characteristics of COVID-19 disease in different age groups, Children (0-19), Adults (20-64|) and Older Adults (65+) and compare whether there were any differences observed. The key findings of this study indicate is that there appears to be a much wider spread of symptoms reported for Children (0-19) than for the Adults (20-64) and Older Adults (65+) groups. Refusal to eat/ Anorexia was the 3rd most common symptom in Children (45%) and was found to be and 14 times higher than in Adults (3.2%) compared to being only 1.99 times higher than in Older Adults (65+) which supportsfindings in previous studies as were discussed in the Literature review which have indicated that although the predominate presentation of children with COVID-19 is asymptomatic, when they are symptomatic, they are more likely than both the Adults (20-64) and Older Adults (65+) age groups to present with gastrointestinal symptoms. This

clinical significance of this findings is that it may be being overlooked as a presenting symptom of COVID-19 within this age group and where regular testing is unavailable or unreliable, and protective measures such as mask wearing being diminished, could contribute to underdiagnosis and underreporting of cases. This would have a detrimental impact on prevention and control of COVID-19 spread within the population as these overlooked but symptomatic individuals similarly to those who are asymptomatic may continue transmitting the infection to others in their respective environments unbeknownst to themselves, their Physicians and Public Health officials and those around them.

Similarly, the presentation of Fever is in the top 2-3 symptoms for all age groups but is much higher for Older Adults than it is for Children and Adults, as is the presentation of Shortness of Breath and Confusion which were indicated as being severe symptoms by WHO (2021), in this study Shortness of Breath was 6.28 times higher in the Older Adults (65+) group than the Children and Adolescents group (9.5%) and 3.57 times higher than in the Adults group (16.7%). Cough was the most common reported symptom across all age groups with the symptoms of Loss of Taste and Smell being one of least commonly reported symptoms across all age groups, but when present was found to be higher in the Adults group than for the Children's group.

The findings in the Literature Review, Chapter III as to (i) why some are more susceptible than others to severe infection and outcome, appears to be due to factors such as gender, age and ethnicity where higher mortality rates were found in Men, the Elderly and Minorities with COVID-19, and the Co-Morbidities listed by the CDC for development of severe COVID-19 infection are also the top NCD's which have the highest mortality rates on their own, yet are also risk factors for increased mortality in those with COVID-19 disease. As well as this, the role of the ACE2 receptor in the pathogenesis of SARS-CoV-2 as the binding site for the S1 subunit of the spike protein which aids in facilitating entry into the human host cell, and the presence of ACE2 receptor protein on the surface of numerous tissues within multiple organ systems within the human body and the potential consequences of RAAS imbalance following ACE/ACE2 disruption leading to a pro-inflammatory response via Angiotensin II, which provides one explanation for why not only different organ systems appear to be affected in different individuals with COVID-19 but also similar findings in those who develop Long COVID after recovery from initial COVID-19 disease. The findings as to (ii) The long term-effects of SARS-CoV-2 infection (Long COVID) in those who recovered from COVID-19 disease was that the most common symptoms were Fatigue, Shortness of Breath and Chest Pain reported in all three studies. Sore Throat, Cough, Myalgia/Arthralgia were reported in two of the three studies, whilst Headache, Loss of Smell, Abdominal Pain, Diarrhea, Loss of Appetite, Dizziness, Somnipathy, Anxiety, Depression, Delirium, Alopecia and new onset Hypertension were each reported in only one of the three studies.

The ongoing COVID-19 pandemic has impacted lives on a global scale, the rapid advancements made in Science and Medicine have allowed for the accelerated production and development of vaccines to provide a significant life-saving layer of protection to the global population and to those most at risk of developing serious, life-threatening symptoms and complications from COVID-19. Overall, what is clearly indicated from the findings of this study and the literature review is the importance of on-going scientific research into SARS-CoV-2 to successfully combat this on-going pandemic, save lives in the process as well as outline preventative measures that can be taken for the successful prevention of similar pandemics in the future.

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