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Review

Biological Psychiatry: GOS

Systemic Inflammatory Biomarkers in DSM-5–Defined Disorders and COVID-19: Evidence From Published Meta-analyses

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ABSTRACT

On March 11, 2020, the World Health Organization declared the outbreak of the novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) as a global pandemic. At the center of SARS-CoV-2 is the activation of inflammatory markers; remarkably, interleukin 6 and C-reactive protein seem to be consistently elevated in patients with SARS-CoV-2. Here, we showed that increased systemic C-reactive protein and interleukin 6 are common biomarkers of both severe COVID-19 and DSM-5–defined disorders. However, it is not known whether patients with psychiatric disorders with preexisting increased interleukin 6 and C-reactive protein are more vulnerable to severe complications of COVID-19 because of the additive inflammatory processes.

https://doi.org/10.1016/j.bpsgos.2022.01.006

On March 11, 2020, the World Health Organization declared the outbreak of the novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) as a global pandemic. The impact of COVID-19 is drastic, infecting more than 250 million people worldwide, killing more than 5 million people (as of November 11, 2021), and causing a significant halt to business and education. With the magnitude of this global crisis, we are also observing increased frequency and extent of mental disorders. The first clue behind the relationship between COVID-19 and neuropsychiatric manifestations was from a case study involving a woman in her late 50s (1). In this study, the woman with a positive test result for SARS-CoV-2 presented with altered mental status, including confusion, lethargy, and disorientation. Building on this finding, several observational studies reported that more than one third of patients with COVID-19 presented with neuropsychiatric manifestations, including dizziness, headache, impaired consciousness, seizure, hallucinations, psychosis, and delirium (2), raising a crucial question of whether the psychiatric patient population exposed to SARS-CoV-2 may be more vulnerable to having a severe COVID-19 phenotype. Indeed, patients with preexisting mood disorders were found to have more severe COVID-19 symptoms and were more likely to be hospitalized and have a higher mortality rate, indicating that they should be viewed as an at-risk cohort (3). While these findings highlight the vulnerability of the psychiatric population to COVID-19, no studies have yet evaluated the biological basis that could potentially explain these clinical observations.

One potential biological process that supports these clinical observations is the preexisting increased systemic inflammation frequently observed in patients with mental disorders. Inflammatory biomarkers are crucial for evaluating systemic inflammation and are well documented to be associated with the severity or rapid progression of COVID-19. Several biomarkers of systemic inflammation, such as C-reactive protein (CRP) and inflammatory cytokines, including interleukins (ILs), interferons, and tumor necrosis factors, are widely studied in COVID-19 and mental disorders. However, studies evaluating the relationship between inflammation, COVID-19, and mental disorders are limited. Here, we aimed to review and gather evidence from previously published systematic reviews and meta-analyses examining CRP and cytokine levels in patients with COVID-19 or patients with mental disorders.

Over the course of the COVID-19 pandemic, five systematic reviews and meta-analyses were published examining cytokine levels in patients with COVID-19. The following search terms on PubMed were used to identify the systematic reviews and meta-analyses: (SARS-CoV-2 OR COVID-19) AND (CRP OR C-reactive protein OR inflammatory cytokines OR cytokines) (Table 1 and Figure 1). We chose to gather evidence from meta-analysis studies because of the unique ability of meta-analyses to combine datasets across multiple independent studies to compute a more reliable statistical significance and effect size. One study reported that IL-6 is significantly elevated in patients with COVID-19 who show adverse clinical presentations (4). Another meta-analysis found elevated levels of CRP, ferritin, and other cytokines such as IL-6, tumor necrosis factor α, interferon γ, IL-8, IL-2, and IL-10 in patients with COVID-19 (5). Another team examining inflammatory markers in nonsevere, severe, and nonsurvivor patients with COVID-19 found increased levels of IL-6, CRP, IL-10, IL-2 receptor, and serum amyloid A in the severe and nonsurvivor patient groups (6). Similarly, in two other meta-analyses, patients with severe disease states showed elevated white blood cell counts, CRP, IL-6, and IL-10, and the nonsurvivor groups expressed even higher levels of these markers (7,8). The

ISSN: 2667-1743

Table 1. Meta-analysis Study Results on the Inflammatory Biomarkers in Patients With COVID-19

Meta-analyses		Results on Inflammatory Biomarkers								
Study	PMID	CRP	IL-6	TNF-α	IFN-γ	IL-1β	IL-8	IL-2	IL-10	sIL-2R
Coomes and Haghbayan, 2020 (4)	32845568	–	↑	–	–	–	–	–	–	–
Akbari *et al.*, 2020 (5)	32735885	↑	↑	↑	↑	→	↑	↑	↑	–
Mahat *et al.*, 2021 (6)	33778183	↑	↑	→	–	–	–	–	↑	↑
Ji *et al.*, 2020 (7)	33217868	↑	↑	→	–	–	–	–	↑	–
Henry *et al.*, 2020 (8)	32286245	↑	↑	–	–	–	↑	–	↑	↑

↑, increase; ↓, decrease; →, no change; –, not reported.

CRP, C-reactive protein; IFN-γ, interferon γ; IL, interleukin; PMID, PubMed identifier; sIL-2R, soluble IL-2 receptor; TNF-α, tumor necrosis factor α.

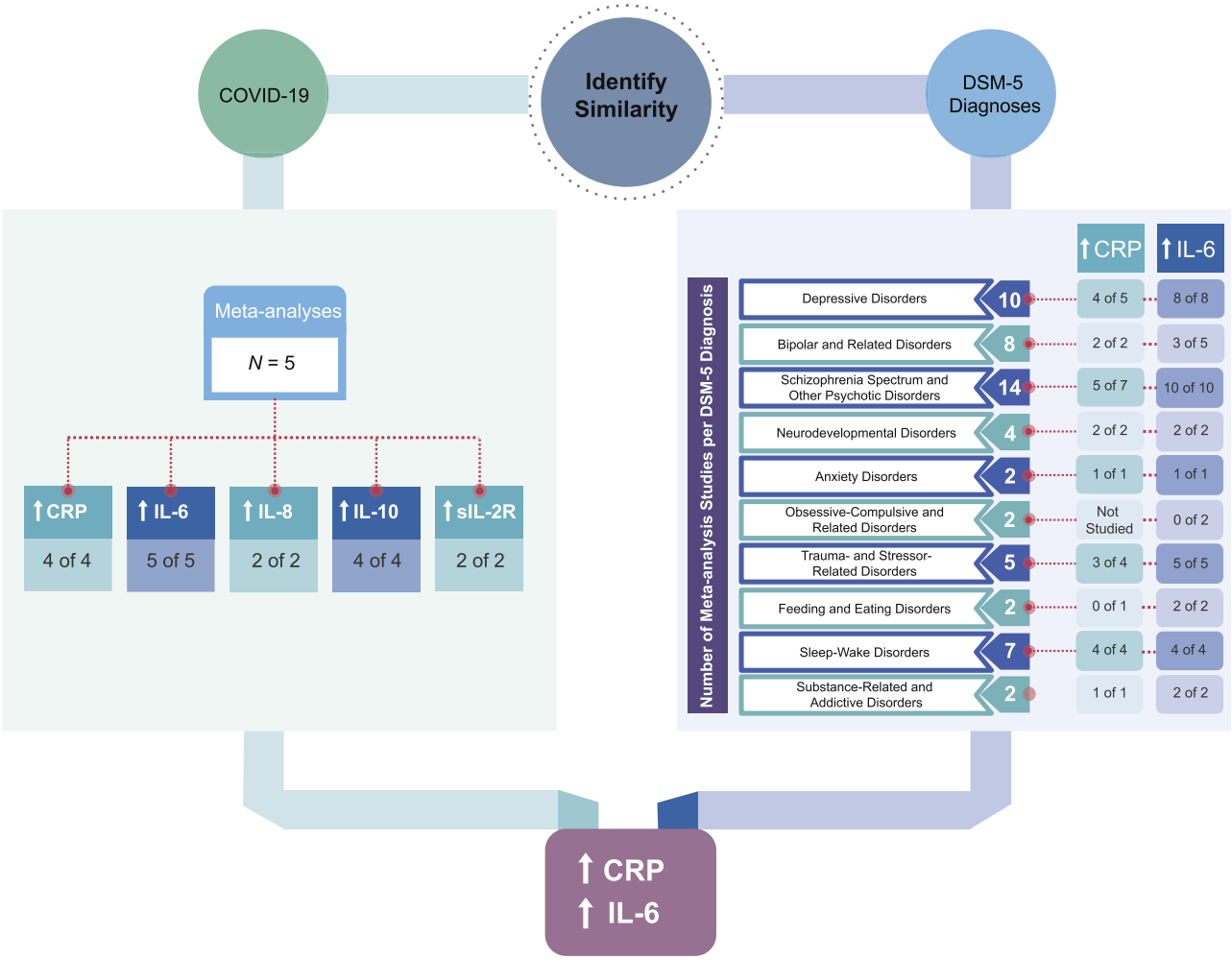

Figure 1. Study workflow on the identification of similarity between severe COVID-19 and DSM-5 diagnoses. The left panel shows the identification of meta-analyses evaluating inflammatory markers in patients with COVID-19 and the number of studies showing increased levels of inflammatory cytokines of the total number of meta-analyses for each cytokine. The right panel shows the number of meta-analysis studies identified across DSM-5–defined psychiatric disorders, along with the number of studies showing an increase in CRP and IL-6 among the total number of studies identified for each DSM-5 diagnosis. Inflammatory markers were compared between severe COVID-19 and DSM-5 diagnoses, leading to the identification of increased CRP and IL-6. CRP, C-reactive protein; IL, interleukin; PMID, PubMed identifier; sIL-2R, soluble IL-2 receptor.

common inflammatory biomarkers found among all these meta-analyses published to date are CRP, IL-6, IL-8, IL-10, and soluble IL-2 receptor. These studies suggest that tracking these inflammatory markers can allow for prediction of COVID-19 severity. However, none of the meta-analyses stratified the COVID-19 patient population by diagnoses of

Table 2. Meta-analysis Study Results on the Inflammatory Biomarkers Across DSM-5 Diagnoses

		Meta-analyses		Results on Inflammatory Biomarkers								
DSM-5 Classification	Patient Group	Study	PMID	CRP	IL-6	TNF-α	IFN-γ	IL-1β	IL-8	IL-2	IL-10	sIL-2R
Depressive Disorders	MDD (youth and adolescents)	Colasanto *et al.*, 2020 (11)	33065836	↑	↑	→	–	–	–	–	–	–
	MDD	Osimo *et al.*, 2020 (12)	32113908	↑	↑	↑	→	↑	↑	↑	↑	↑
	Drug-naïve first-episode MDD	Çakici *et al*, 2020 (13)	32330592	↑	↑	↑	↑	↑	↓	↑	→	–
	MDD	Osimo *et al.*, 2019 (14)	31258105	↑	–	–	–	–	–	–	–	–
	MDD (elderly)	Ng *et al.*, 2018 (15)	30104698	→	↑	→	–	↑	–	–	–	–
	MDD	Köhler *et al.*, 2017 (16)	28122130	–	↑	↑	↓	→	→	–	↑	↑
	MDD (acutely ill)	Goldsmith *et al.*, 2016 (17)	26903267	–	↑	↑	↓	→	–	→	↑	↑
	MDD (chronically ill)	Goldsmith *et al.*, 2016 (17)	26903267	–	↑	→	–	→	→	↓	→	→
	MDD	Dowlati *et al.*, 2010 (18)	20015486	–	↑	↑	→	→	→	→	→	–
	MDD	Howren *et al.*, 2009 (19)	19188531	↑	↑	–	–	–	–	–	–	–
Bipolar and Related Disorders	BD	Solmi *et al.*, 2021 (20)	34332041	↑	↑	↑	–	→	–	–	–	–
	BD	Fernandes *et al.*, 2016 (21)	27838212	↑	–	–	–	–	–	–	–	–
	BD mania	Goldsmith *et al.*, 2016 (17)	26903267	–	↑	↑	–	–	–	–	→	↑
	BD euthymic (chronically ill)	Goldsmith *et al.*, 2016 (17)	26903267	–	↑	→	→	↑	–	→	↑	↑
	BD depression (chronically ill)	Goldsmith *et al.*, 2016 (17)	26903267	–	→	→	–	–	–	–	→	–
	BD	Dargél *et al.*, 2016 (22)	25742201	↑	–	–	–	–	–	–	–	–
	BD	Munkholm *et al.*, 2013 (23)	23768870	–	→	↑	→	→	→	→	→	↑
	BD	Modabbernia *et al.*, 2013 (24)	23419545	–	↑	↑	→	↑	→	→	↑	↑
Schizophrenia Spectrum and Other Psychotic Disorders	Drug-naïve first-episode SCZ	Çakici *et al.*, 2020 (13)	32330592	↑	↑	↑	↑	→	↑	→	→	–
	High-risk psychosis	Park and Miller, 2019 (25)	30967316	→	↑	→	→	↓	→	–	→	–
	First-episode psychosis	Fraguas *et al.*, 2019 (26)	30169868	→	↑	↑	→	→	→	→	→	→
	SCZ spectrum disorders	Bora, 2019 (27)	31284882	↑	–	–	–	–	–	–	–	–
	SCZ	Wang *et al.*, 2017 (28)	29088880	↑	–	–	–	–	–	–	–	–
	SCZ	Fernandes *et al.*, 2016 (29)	26169974	↑	–	–	–	–	–	–	–	–
	First-episode psychosis	Goldsmith *et al.*, 2016 (17)	26903267	–	↑	↑	↑	↑	↑	→	↑	↑
	SCZ (acutely ill)	Goldsmith *et al.*, 2016 (17)	26903267	–	↑	↑	↑	↑	↑	→	↓	↑
	SCZ (chronically ill)	Goldsmith *et al.*, 2016 (17)	26903267	–	↑	↑	↓	↑	–	→	→	↑
	SCZ	Miller *et al.*, 2014 (30)	23428789	↑	–	–	–	–	–	–	–	–
	Medication-naïve first-episode psychosis	Upthegrove *et al.*, 2014 (31)	24704219	–	↑	↑	→	↑	–	→	–	↑
	SCZ (acutely relapsed)	Miller *et al.*, 2011 (32)	21641581	–	↑	↑	↑	–	↑	→	↓	→
	First-episode psychosis	Miller *et al.*, 2011 (32)	21641581	–	↑	↑	↑	↑	–	→	–	↑
	SCZ	Potvin *et al.*, 2008 (33)	18005941	–	↑	→	–	→	–	→	–	↑
Neurodevelopmental Disorders	ASD	Yin *et al.*, 2020 (34)	32272227	↑	–	–	–	–	–	–	–	–
	ASD	Nadeem *et al.*, 2020 (35)	32448119	↑	–	–	–	–	–	–	–	–
	ASD	Saghazadeh *et al.*, 2019 (36)	31125917	–	↑	↑	↑	↑	→	→	–	→
	ASD	Masi *et al.*, 2015 (37)	24934179	–	↑	→	↑	↑	↑	–	→	–

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Table 2. Continued

DSM-5 Classification	Patient Group	Meta-analyses		Results on Inflammatory Biomarkers								
		Study	PMID	CRP	IL-6	TNF-α	IFN-γ	IL-1β	IL-8	IL-2	IL-10	sIL-2R
Anxiety Disorders	GAD	Costello *et al.*, 2019 (38)	31326932	↑	–	↑	↑	–	–	–	–	–
	Anxiety	Renna *et al.*, 2018 (39)	30199144	–	↑	↑	→	↑	→	→	→	–
Obsessive-Compulsive and Related Disorders	OCD	Cosco *et al.*, 2018 (40)	30382535	–	→	→	→	→	–	–	→	–
	OCD	Gray and Bloch, 2012 (41)	22477442	–	→	→	–	↓	–	–	–	–
Trauma- and Stressor-Related Disorders	PTSD	Yang and Jiang, 2020 (42)	32158005	↑	↑	↑	↑	↑	→	↑	→	–
	Childhood sexual abuse	D'Elia *et al.*, 2018 (43)	30127754	↑	↑	↑	–	–	–	–	–	–
	PTSD	Renna *et al.*, 2018 (39)	30199144	–	↑	↑	→	↑	→	→	→	–
	Childhood trauma	Baumeister *et al.*, 2016 (44)	26033244	↑	↑	↑	–	–	–	–	–	–
	PTSD	Passos *et al.*, 2015 (45)	26544749	→	↑	→	↑	↑	→	→	→	→
Feeding and Eating Disorders	Anorexia and bulimia nervosa	Dalton *et al.*, 2018 (46)	29906710	–	↑	↑	–	→	–	–	–	–
	Anorexia nervosa	Solmi *et al.*, 2015 (47)	25462897	↓	↑	↑	–	↑	–	–	–	–
Sleep-Wake Disorders	Narcolepsy	Mohammadi *et al.*, 2020 (48)	32315956	–	↑	↑	–	–	→	–	→	–
	OSA	Van der Touw *et al.*, 2019 (49)	30908094	↑	–	–	–	–	–	–	–	–
	OSA	Li and Zheng, 2017 (50)	28187003	–	–	↑	–	–	–	–	–	–
	OSA	Li *et al.*, 2017 (51)	28489776	↑	–	–	–	–	–	–	–	–
	OSA	Zhong *et al.*, 2016 (52)	26564171	–	↑	–	–	–	–	–	–	–
	Sleep disturbance	Irwin *et al.*, 2016 (53)	26140821	↑	↑	→	–	–	–	–	–	–
	OSA	Nadeem *et al.*, 2013 (54)	24127144	↑	↑	↑	–	–	↑	–	–	–
Substance-Related and Addictive Disorders	Alcohol use disorders	Adams *et al.*, 2020 (55)	32805393	–	↑	↑	→	→	↑	→	→	→
	Substance use disorders	Wei *et al.*, 2020 (56)	32533781	↑	↑	↑	→	→	↑	→	↑	–

↑, increase; ↓, decrease; →, no change; –, not reported.

ASD, autism spectrum disorder; BD, bipolar disorder; CRP, C-reactive protein; GAD, generalized anxiety disorder; IFN-γ, interferon γ; IL, interleukin; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; OSA, obstructive sleep apnea; PMID, PubMed identifier; PTSD, posttraumatic stress disorder; SCZ, schizophrenia; sIL-2R, soluble IL-2 receptor; TNF-α, tumor necrosis factor α.

mental disorders or reported the prevalence of mental disorders, although some individual studies did attempt this analysis. One research group evaluated CRP levels in COVID-19 survivors with a previous diagnosis of mental disorders and did not find a difference compared with those without a diagnosis of mental disorders (9). However, CRP measurements were collected from the patients at a 1-month follow-up, which may not reflect the active disease state of COVID-19. Preliminary findings from a cross-sectional survey study identified no changes in IL-6, IL-8, IL-10, tumor necrosis factor α, and CRP in patients with COVID-19 stratified by with or without psychiatric symptoms (10). However, higher levels of IL-1β were significantly associated with a higher score of depression, anxiety, and insomnia. Even then, the authors did not comment on whether these patients had a prior diagnosis of mental disorders before contracting SARS-CoV-2. It remains unclear which inflammatory biomarkers are associated with a dual diagnosis of COVID-19 and mental disorders.

To understand whether inflammatory biomarkers associated with the severity of COVID-19 are also reported in patients with mental disorders, we compared the COVID-19 meta-analysis findings with previously published meta-analyses of inflammatory biomarkers for all disorders defined by the DSM-5. The following search terms on PubMed were used to identify the systematic reviews and meta-analyses for DSM-5–defined disorders: (CRP OR C-Reactive Protein OR inflammatory cytokines OR cytokines) and (bipolar disorder OR major depressive disorder OR depression OR schizophrenia OR psychosis OR psychotic disorders OR neurodevelopmental disorders OR anxiety disorders OR obsessive-compulsive disorder OR OCD OR post-traumatic stress disorder OR PTSD OR anorexia OR bulimia OR sleep disorder OR obstructive sleep apnea OR substance use disorder OR addictive disorder OR addiction). We identified a total of 56 meta-analysis studies of systemic inflammatory biomarkers across 10 DSM-5 classifications (10 for depressive disorders, 8 for bipolar and related disorders, 14 for schizophrenia spectrum and other psychotic disorders, 4 for neurodevelopmental disorders, 2 for anxiety disorders, 2 for obsessive-compulsive and related disorders, 5 for trauma- and stressor-related disorders, 2 for feeding and eating disorders, 7 for sleep-wake disorders, and 2 for substance-related and addictive disorders) (Figure 1). We included all meta-analysis studies for reproducibility purposes. While each DSM-5 classification displayed a unique inflammatory profile, IL-6 and CRP were observed to be consistently shared across all DSM-5 disorders except for obsessive-compulsive disorders and feeding and eating disorders for CRP (Table 2) (11–56). Our observation of increased IL-6 and CRP from this parallel comparison of meta-analyses would need to be further investigated in future comparative cross-sectional and longitudinal studies using patient samples to better understand whether IL-6 and CRP are commonly elevated in COVID-19 and mental disorders. Examining whether these inflammatory markers are associated with symptom severity of COVID-19 and mental disorders would also be crucial to understand whether high inflammation may be a potential mechanism for the severe outcomes seen in patients with mental disorders infected by COVID-19.

Chronic inflammation, a state of persistent low-grade inflammation in the absence of acute infection, is commonly associated with mental disorders. Several studies have shown that high levels of inflammatory molecules in the blood can induce significant permeability to the blood-brain barrier (57). When this occurs, these inflammatory molecules can enter the brain through the blood-brain barrier, potentially disrupting the neural circuits that control mood and behavior, leading to symptoms of mental disorders. The causal link between cytokines and psychiatric symptoms has already been demonstrated in human and animal studies showing that administration of interferon alpha leads to sickness behaviors and depressive-like symptoms (58). Based on these previous findings, it is plausible that synergistic interactions between chronic inflammation and acute inflammation caused by SARS-CoV-2 infection could potentially exacerbate the severity of COVID-19 within the psychiatric patient population. So far, analyses of the cerebrospinal fluid have shown increased levels of IL-6 in patients with COVID-19, major depressive disorder, and schizophrenia, suggesting potential effects on the brain. While studies have shown that peripheral inflammation can induce effects on the brain, it remains unclear whether this is the underlying biological mechanism that contributes to the vulnerability of psychiatric patients to severe COVID-19 or vulnerability of patients with COVID-19 to psychiatric manifestations. Future longitudinal studies and validation studies using animal models of COVID-19 and mental disorders are needed to establish this causal relationship.

COVID-19 is a heterogeneous disease with a variety of effects and manifestations on the immune system's inflammatory response. By examining evidence from meta-analyses, most of the studies reviewed happened to conclude that IL-6 and CRP are increased in mental disorders and COVID-19 independently. It remains unknown whether mental disorders with preexisting increased IL-6 and CRP may be more vulnerable to severe complications of COVID-19 because of the additive inflammatory processes. In addition, patients with mental disorders often have clinical comorbidities such as obesity, which might also increase the inflammation levels and contribute to more severe COVID-19–related complications. Needless to say, there is a need to evaluate patients with COVID-19 with a clinically confirmed mental disorder, at high risk for a mental disorder, and those experiencing psychosis and mood changes. Inflammatory indicators could help identify critical patients with COVID-19 and facilitate the initiation of a treatment plan. Perhaps this would be through monitoring inflammatory markers such as IL-6 and CRP. Early identification of potential hyperinflammation in the psychiatric patient population with COVID-19 may be crucial in alleviating the mental health conditions associated with the COVID-19 pandemic.

ACKNOWLEDGMENTS AND DISCLOSURES

AD was supported by a Precision Medicine Fellowship, Ontario Graduate Scholarships, and a University of Toronto Fellowship. ACA holds a Canada Research Chair Tier 2 in Molecular Pharmacology of Mood Disorder and a grant from the Canadian Institutes of Health Research (Grant No. 505547).

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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Received Sep 15, 2021; revised and accepted Jan 3, 2022.

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