COVID-19 Severity and Associated Laboratory Tests Abnormalities in Glucose-6-Phosphate Dehydrogenase Deficiency Patients: A Systematic Review and Meta-Analysis

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Abstract

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common enzymatic disorder. This situation leads to an increase in reactive oxygen species (ROS) within the body, causing tissue damage and hemolytic anemia. COVID-19 affects individuals differently, with those with chronic conditions at a higher risk of experiencing a more severe outcome. This research aimed to provide a summary of the symptoms, test results, and seriousness of COVID-19 in individuals with G6PD deficiency to enhance medical care. This systematic review followed the PRISMA-P guidelines. MeSH terms, Google Sites, and books were used to identify keywords for G6PD and COVID-19. Various databases were searched without time or location restrictions and manual searches were conducted. Eligibility criteria included observational studies in English on G6PD deficiency and COVID-19. Data extraction and quality assessment were done using specific tools and statistical analysis was performed using R. Eight selected studies that met the criteria were analyzed in this systematic review to investigate the relationship between G6PD deficiency and COVID-19 outcomes. The studies that were included examined a variety of clinical factors and results related to the severity of COVID-19 in individuals with G6PD deficiency. The results showed varying effects on various aspects of disease severity and clinical indicators. Liver function tests and complete blood counts showed notable differences between COVID-19 patients with G6PD deficiency and those without. Consistently, G6PD-deficient individuals showed increased levels of inflammatory markers and metabolic disturbances, indicating possible effects on disease development. In conclusion, our study highlights the essential role of laboratory tests in understanding COVID-19 severity, especially in individuals with G6PD deficiency. Future research should investigate the intricate underlying mechanisms.

Introduction

The global coronavirus disease (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in 2019. More than 775 million people worldwide have been infected by COVID-19, with over 7 million fatalities reported,[1] The progression of the illness differs, with 30.8% of patients showing no symptoms, while others experience a more serious illness with a higher chance of death. People who are 60 years old and older, along with individuals who have chronic conditions like diabetes, high blood pressure,

respiratory illnesses, heart diseases, hemoglobin disorders, and anemia, are more prone to experiencing a severe progression.[2-7]

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a prevalent enzymopathy inherited in an X-linked recessive manner that affects more than 400 million individuals globally.[8] G6PD protects cells against oxidative damage by generating substances that counteract reactive oxygen species (ROS). ROS accumulation in individuals with G6PD deficiency can lead to tissue damage, particularly during periods of oxidative stress.[9] Erythrocytes are particularly vulnerable to ROS, because they are unable to regenerate mature cell proteins. This vulnerability can lead to sudden hemolytic anemia under oxidative stress and chronic hemolytic anemia.[9] Certain food items such as fava beans, medications, and diseases such as viral infections that lead to ROS production through inflammation can induce oxidative stress.[10]

Multiple factors influence the progression of COVID-19 in individuals with G6PD deficiency. Accumulation of ROS creates conditions that promote viral replication, which may worsen the disease.[11] Additionally, G6PD deficiency can impact the immune system by reducing the function of neutrophils, cytokines, and inflammasomes, increasing vulnerability to COVID-19 and resulting in more critical illness progression.[12] Anemia decreases the oxygen supply to tissues, which can lead to respiratory system dysfunction and higher oxygen needs in individuals with COVID-19. As the illness advances, chronic lack of oxygen can result in ischemia of peripheral tissues or failure of multiple organs.[13]

Previous reviews have examined the severity, prognosis, and incidence of COVID-19 in individuals with anemia and other anemia-causing disorders, such as sickle cell disease and thalassemia.[2,6,7,14,15] This systematic review intends to provide a summary of how COVID-19 manifests clinically, its impact on lab results, and the level of severity in individuals with G6PD deficiency. Therefore, physicians should be able to make educated decisions and develop treatment plans and protocols for managing COVID-19 in G6PD-deficient patients.

Considering the potential impact of G6PD deficiency on the development of COVID-19, it is essential to consider this condition when providing care to affected patients. Further research is needed to fully understand these implications and to develop targeted treatment strategies. By shedding light on this interaction, our evaluation sought to improve patient outcomes and encourage superior clinical practice.

Methods

This review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P).[16]

Search Strategy

Using MeSH terms, Google sites, and books as outlined in (supplement1), the appropriate search keywords for G6PD and COVID-19 were identified. The investigation was carried out across the Scopus, PubMed, CINAHL complete, and Cochrane library databases from the beginning to June 2024 with no limitations on time or location. We also conducted manual searches on additional search engines for potential studies to include, as well as reviewed reference lists of retrieved articles and review articles. The search strategy was peer reviewed in accordance with PRESS guidelines.[17]

Eligibility Criteria

All observational studies that satisfied the specified requirements were incorporated, including:[1] examining the severity and/or related laboratory abnormalities in G6PD deficient individuals upon contracting COVID19, and [2] being conducted in English. Cases and controls varied among the studies included based on the study design and were determined individually for each study. Each study included diagnostic methods for both the disorders. Reviews, editorials, letters to the editor, opinions, conference abstracts, books, posters, theses, case reports, case letters, and case series were excluded.

Screening and Data Extraction

All studies gathered from each database were transferred to Rayyan.ai, an online tool used to detect and remove duplicate records.[18] Subsequently, three separate authors evaluated the titles, abstracts, and keywords of the remaining publications to determine whether they should be included in this review. Next, the complete texts of publications that passed the initial screening were carefully evaluated to ensure that they met the requirements for inclusion in the review. Differences were settled by agreement or discussion with a third evaluator. Two additional reviewers conducted data extraction, with a third author assigned to address any discrepancies that arose. Information was gathered from the included studies (Supplement 2).

Quality assessment

The JBI critical appraisal checklists were used to evaluate the methodological quality of the cohort and case-control studies included in Supplement 3.

Statistical Analysis

We used R version 4.4.0 to perform the meta-analysis. Statistical significance was set to 0.05. Random effects models were used, considering the differences in sample size among the studies. Heterogeneity was assessed using Cochran's Q test and quantified with the I^2 statistic, which estimates the proportion of variability attributable to heterogeneity rather than sampling error. An I^2 value below 50% was interpreted as low heterogeneity, 50–75% as moderate, and greater than 75% as high. We set the significance level for heterogeneity at $p = 0.1$, as it is more conservative in detecting true heterogeneity in meta-analyses with fewer studies. Effect sizes, including mean differences (MDs) for continuous variables and odds ratios (ORs) for dichotomous outcomes, were calculated with 95% confidence intervals (CIs). The statistical significance level for the meta-analysis was set to $p < 0.05$. Forest plots were generated to visualize the pooled estimates, confidence intervals, and heterogeneity among studies. The clinical relevance of the findings was interpreted in the context of the heterogeneity and the magnitude of the effect size. Significant results were discussed with a focus on their implications for patient management and understanding the pathophysiological link between G6PD deficiency and COVID-19.

Results

A search of multiple databases yielded 253 records. The databases included PubMed (83 records), CINAHL (19 records), and Scopus (151 records), with no relevant records found in Cochrane. Of the 168 records passed for the screening of titles and abstracts, only 37 records that linked G6PD deficiency and COVID-19 were subjected to a more detailed full-text screening. Finally, eight studies were selected for the systematic review after a thorough screening process, including four for the meta-analysis, to examine the connection between G6PD deficiency and COVID-19 (Figure 1).

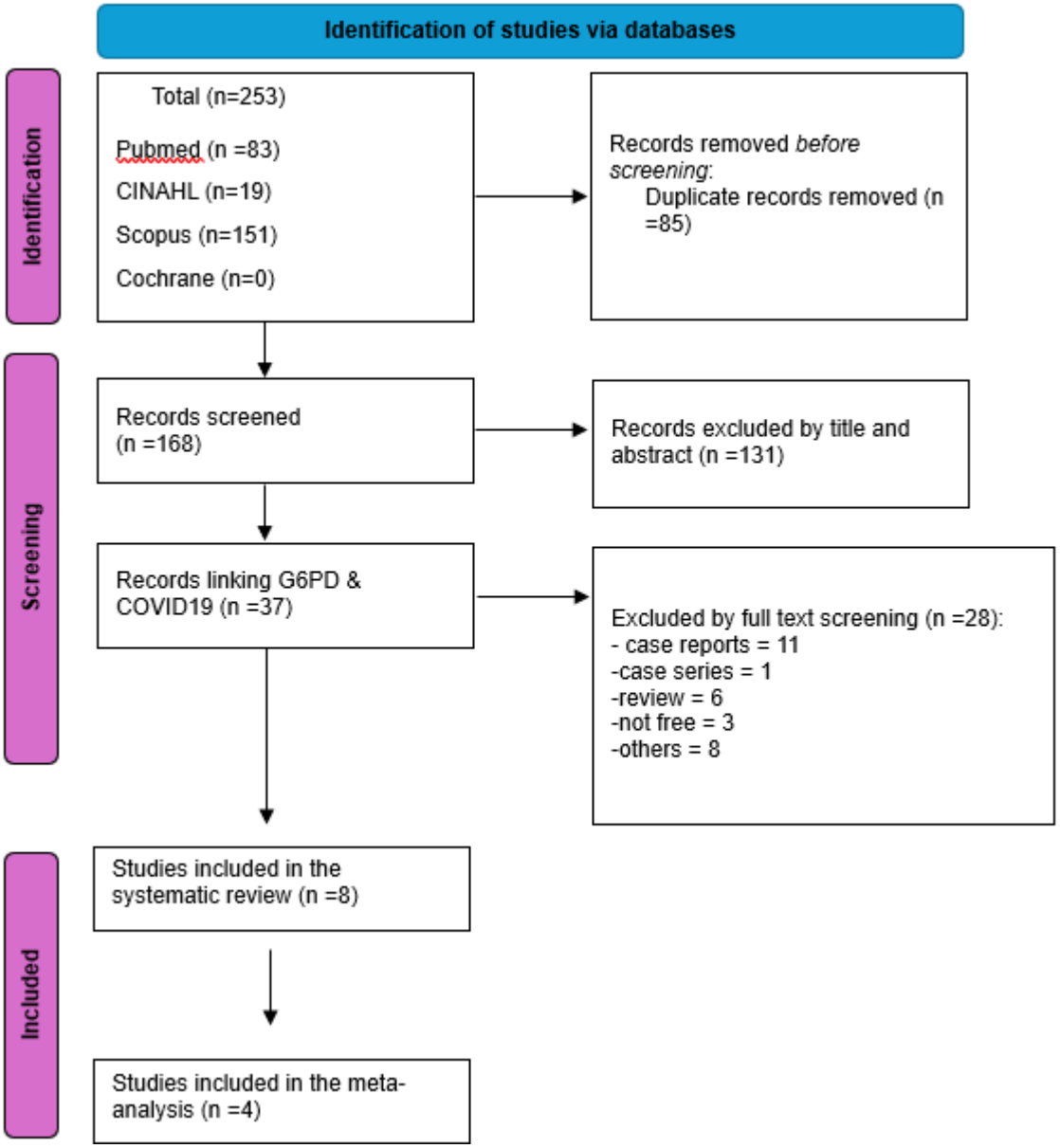

Figure 1: PRISMA Chart for COVID-19 severity and associated laboratory tests abnormalities in Glucose-6-Phosphate Dehydrogenase deficiency patients: A Systematic Review and Meta-Analysis

Study's Methodologies

All eight studies included in this systematic review examined the relationship between G6PD deficiency and COVID-19 using various methodologies to classify the study and control groups. All studies consistently used PCR tests to diagnose COVID-19, ensuring uniformity in identifying infected individuals.[19-26] The classification of G6PD deficiency has also been standardized across most studies, with documented laboratory tests or recorded activity levels being common methods for confirmation.[22-26] In terms of group categorization, several studies have adopted a three-group model: participants with COVID-19 and G6PD deficiency, participants with COVID-19 without G6PD deficiency, and healthy controls.[22,24] This approach allowed for a comprehensive comparison of different health statuses. Notably, Alotaibi et al. (2023) and Mushtaq et al. (2022) separately included groups with either COVID-19 or G6PD deficiency, providing an analysis of each condition independently and in combination.[19,21] Detailed information found in table 1.

Table 1: Studies characteristics.

Study ID	Journal	Study design	Location	Methodology	Studied factors
Alotaibi et al. (2023)[27]	Viruses 2023, 15, 1224	Retrospective Study	Saudi Arabia	The study group included every patients who tested G6PD positive and COVID 19 positive. While the control groups were two groups: group 1: COVID +v pts, and Group 2: G6PD +v pts. Information regarding the G6PD status was based on a standard allergy questionnaire taken at admission. COVID-19 infection was tested using polymerase chain reaction tests.	Age, gender, coagulation profile (PT,PTT),d-DIMER, Fibrinogen, LHD, total bilirubin, ferretin, Liver function test, Albumin, creatinin, BUN, blood Glucose test, CRP.
Mushtaq et al.(2022)[28]	QATAR MEDICAL JOURNAL	retrospective analysis	Qatar	The study groups were COVID-19 positive patients whom were divided into two groups: with and without G6PD deficiency while COVID-19 negative patients with or without G6PD deficiency from the community were used as control groups. Reverse transcription–PCR tests for SARS-CoV-2 was used as a diagnostic test for COVID-19.	Age, gender, WHO criteria severity of COVID-19 infection (SpO2,PaO2/FiO2,Respiratory rate, lung infiltrate), Age, WBC,HB, HCT, MCV,PLATLET, ANC, DIFFERENTIAL OF WBC, Bilirubin.
Parnasa et al.(2023)[29]	IMAJ-VOL 25	case control	Israel (Palestine)	The criteria of the study group was every patients who was G6PD positive and COVID 19 positive, While COVID-19 POSITIVE, G6PD NEGATIVE was included as control group. The G6PD deficiency group consisted of patients with a documented G6PD deficiency or a recorded laboratory test of G6PD activity performed in LHS, resulting in a measurement below 4 U/g Hg.	Age, gender, WHO criteria severity of COVID-19 infection (SpO2, PaO2/FiO2,Respiratory rate, lung infiltrate),presence of co-morbidities, duration of hospitalization, age, ICU admission, mortality rate from covid-19.
Youssef et al.(2021)[30]	Springer Nature - PMC COVID-19 Collection	Retrospective cohort / case series	Saudi Arabia	G6PD was considered low if the recorded values were below the laboratory cut-off value of 9.6 U/g Hb; < 4.5 was considered severe, values between 4.5 and 9.6 as mild, and all other values as normal. Normal cohorts (where the G6PD values were > 9.6).The reverse-transcriptase–polymerase-chain-reaction (RT-PCR) for SARS-CoV2 from samples obtained from the nasopharyngeal swab was used as a tool to diagnose COVID-19	Age, gender, Criteria used for detecting the severity of pneumonia, including: Need for supplemental oxygen / Length of time on mechanical ventilation / PaO2/FiO2 ratio (ratio of partial pressure of oxygen to fraction of inspired oxygen) / Hemoglobin level /

					Hematocrit / Days on mechanical ventilation
Al-lehebe et al.(2022)[31]	Egyptian Journal of Chemistry	retrospective analysis	Qatar	There was three groups: Group 1(study group): Participants with Covid-19 infection associated with G6PDd Group 2: Covid-19 patients with any chronic diseases, Group 3: Healthy control. The activity of G6PD was measured by using a standard technique to quantitative testing using a G6PD analysis- Kit (Randox-Laboratory, Crumlin, Antrim, UK) according to the scientific group's recommendations. A rapid and molecular test was used as a diagnostic tool to detect COVID-19 infection.	Age, gender, Hb, PCV, total WBC, Ferretin, GOT,GPT,LDH,ALP.
Israel et al.(2023)[32]	CID 2023:77 (1 October)	retrospective cohort	Israel(Palestine)	The study included three groups as follow: Group 1(study group): Participants with Covid-19 infection associated with G6PDd Group 2: Covid-19 patients with any chronic diseases Group 3: Healthy with no G6PDd or Covid 19 infection. The control group was randomly selected among individuals without G6PD deficiency to match to G6PD-deficient individuals on gender, age, socioeconomic status category, and ethnic group, with a ratio of 10 controls for each included G6PD-deficient individual. The G6PD deficiency group consisted of patients with a documented G6PD deficiency or a recorded laboratory test of G6PD activity performed in LHS, resulting in a measurement below 4 U/g Hg.The diagnosis of COVID_19 assessed by the presence of a positive polymerase chain reaction laboratory test or recorded diagnosis of COVID-19 infection), presence of long COVID-19 (identified by the coded diagnosis "late effect of COVID-19 infection" recorded during a medical encounter), and COVID-19–related hospitalization and mortality events (extracted from the national COVID-19 database maintained by the Israeli Ministry of Health).	Age, gender, socioeconomic status, Co-morbidities (hypertension, DM), number of COVID-19 episodes.
Kumar et al.(2021)[33]	Scientific Reports	case control	Bahrain	The criteria of the study group was any participants Above 18 years of age, had a diagnosis of COVID-19 disease had G6PDd. Patients with intermediate levels of G6PD were not considered as having the exposure of interest.While the criteria of control group was any participants who was Above	Age, gender, presence of sickle cell disease, presence of co-morbidities(DM, CVD, HTN, asthma, COPD,CKD, other chronic lung disease),symptoms of

				18 years of age, had a diagnosis of COVID-19 disease and hadn't G6PDd. Fluorescence spot test using whole blood was used to diagnose G6PD deficiency .COVID -19 infection was diagnosed By a polymerase chain reaction (PCR) test of a nasopharyngeal sample. The PCR test was conducted using Thermo Fisher Scientific (Waltham, MA) TaqPath 1-Step RT-qPCR Master Mix, CG on the Applied Biosystems (Foster City, CA) 7500 Fast Dx RealTime PCR Instrument. The assay used and targeted the E gene. If the E gene was detected, the sample was then confirmed by RdRP and N genes. The E gene Ct value was reported and used in this study. Ct values > 40 were considered negative.	COVID-19 on admission, chest radiographic findings, disease severity on admission, Requirement of non-invasive ventilation, intubation or death.
Elsea et al.(2023)[34]	JAMA Network Open	retrospective cohort	United states	G6PD deficient who had a positive molecular PCR-SARS-CoV-2 test or historical positive test in VHA clinical notes from February 15, 2020, to January 1, 2021 where included as study group. Not G6PD deficient who had a positive molecular PCR-SARS-CoV-2 test or historical positive test in VHA clinical notes from February 15, 2020, to January 1, 2021 were included as control group. quantitative enzyme activity testing was used to diagnose G6PD deficiency. And PCR-SARS-CoV-2 test was used to diagnose COVID-19 infection.	Age, gender, ethnicity, the presence of co-morbidities, COVID-19 severe illness parameters as defined by the Centers for Disease Control and Prevention: hospitalization, need for mechanical ventilation and/or intensive care unit admission, or in-hospital mortality after a positive SARS-CoV-2 test.

Studied Factors

The eight studies included in this systematic review examined a variety of factors related to G6PD deficiency and COVID-19 outcomes, with several common factors assessed across the studies. Age and sex were universally considered to provide a demographic baseline for the analysis. Many studies have included measures of disease severity, such as the WHO criteria, which encompassed SpO2, PaO2/FiO2 ratios, respiratory rate, and lung infiltrates.[21,26] Specific clinical markers were frequently evaluated, including coagulation profiles (PT, PTT), D-dimer, fibrinogen, liver function tests (AST, ALT), total bilirubin, albumin, creatinine, BUN, and blood glucose levels, with CRP often used as an indicator of inflammation.[19] Some studies have investigated hematological parameters, such as white blood cell counts (WBC), hemoglobin (HB), hematocrit (HCT), mean corpuscular volume (MCV), platelet counts (PLT), and differentials of WBCs.[21,24]

Other notable factors included the presence and impact of comorbidities like hypertension, diabetes mellitus (DM), cardiovascular disease (CVD), asthma, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), and other chronic lung diseases.[20,22,25] The severity of pneumonia was assessed using criteria such as the need for supplemental oxygen, duration of mechanical ventilation, and PaO2/FiO2 ratios.[23] In addition, some studies have measured lactate dehydrogenase (LDH), ferritin, and albumin levels.[19,24] Detailed information found in table 1

Participant's Characteristics

Participant characteristics varied widely across studies, with notable differences and similarities. Age ranges or mean ages were frequently reported, such as in Mushtaq et al. (2022), where the mean ages ranged from 46 to 51 years across different groups. Parnasa et al. (2023) and Israel et al. (2023) provided mean ages around 52 years and 28 years, respectively, reflecting diverse age demographics. However, some studies, including Alotaibi et al. (2023), Youssef et al. (2021), and Elsea et al. (2023) did not specify age details.

Gender distribution varied, with studies such as Alotaibi et al. (2023) showing nearly equal proportions of males and females, while others such as Israel et al. (2023) and Kumar et al. (2021) skewed towards more males. Ethnicity data, available in several studies, highlighted diverse populations, including Saudi and non-Saudi participants (Alotaibi et al., 2023), and detailed breakdowns such as African Americans, Caucasians, Hispanics, and Asians (Youssef et al., 2021; Israel et al., 2023).

Comorbidities such as heart disease (Parnasa et al., 2023) and conditions such as diabetes mellitus, hypertension, obesity, and previous malignancies (Youssef et al., 2021) were noted across studies, influencing outcomes. These factors collectively shaped the demographic and health profiles of the participants in relation to G6PD deficiency and COVID-19 outcomes. Detailed information found in table 2.

Table 2: Participants' characteristics.

Study ID/REF	Age	Sex distribution	Ethnicity	Co-morbidities and confounding factors
Alotaibi et al. (2023)[27]	N/A	# and % Female: 22273(51.658%) # and % Males: 20837 (48.334%)	Saudi and Non- Saudi participants included in the study	Age
Mushtaq et al.(2022)[28]	Study group (mean) - COVID-19 +ve and normal G6PD activity = (50.5) y (SE:0.83) - COVID-19 +ve and G6PD deficiency = (46) y (SE:1.90) Control group (mean) - COVID-19 -ve and G6PD deficient = (51) y (SE:0.65) - COVID-19 -ve and normal G6PD activity = (48.1) y (SE:0.86)	N/A	N/A	Age
Parnasa et al.(2023)[29]	Study group mean (SD) - (G6PD deficient) = 52.2 (20) y - Control group mean (SD) (G6PD sufficient) = 52.8 (22.6) y	# and % Females Study group - G6PD deficient: 51(43.6%) Control group - G6PD sufficient: 1891 (48.1%) # and % Male Study group - G6PD deficient: 66 (56.4%) Control group - G6PD sufficient: 2038 (51.9%)	N/A	Heart disease, Age
Youssef et al.(2021)[30]	N/A	% Male: 50% % Female: 50%	African American Caucasian Hispanic Asian	Age, Sex, Race/ Ethnicity, DM, HTN, Obesity (BMI >36),previous malignancy.

Al-lehebe et al.(2022)[31]	Mean= 40.01 y	# and % Females Study group COVID-19 +ve with G6PDd: 22 (51.16%) Control group COVID-19 +ve with any chronic diseases: 27 (52.94%) Healthy controls: 19 (47.5%) # and % Males Study group COVID-19 +ve with G6PDd:21 (48.84%) Control group COVID-19 +ve with any chronic diseases: 24 (47.06%) Healthy controls:21 (52.5%)	N/A	Age,Sex,G6PD activity, Lab values(GOT,GPT,ALP,LDH,HB,PCV,WBC),and Heart disease, cancer, HTN, respiratory issues, gastrointestinal issues, DM
Israel et al.(2023)[32]	Study group mean (SD) - G6PD deficient group = 28.3(22.2) y Control group mean (SD) - Matched Control group = 28.3 (22.1) y	% Females Study group G6PD deficient group: 1935 (32.3%) Control group Matched Control group: 19 350 (32.3%) # and % Males Study group G6PD deficient group: 4061 (67.7%) Control group Matched Control group: 40 610 (67.7%)	Arab, General, Ultra-Orthodox	HTN, Sex, Age, Ethnicity.

Kumar et al.(2021)[33]	Mean =45.9 y	# and % Males: Study group G6PDd present: 94 (53.7%), Control group G6PDd absent: 963 (59.6%)	Bahraini nationality Other nationalities	DM, Sickle Cell Disease, Cardiovascular Disease, HTN, Asthma,COPD,CKD,Other Chronic Lung Disease (Not asthma nor COPD),Age, sex(male), Bahraini nationality, medication(Hydroxychloroquine, Azithromycin,Kaletra,Ribavirin,Steroids,Toclizumab),Convalescent plasma transfusion
Elsea et al.(2023)[34]	N/A	# Males:: 3868 # Females: 943	Black, White, or other [self-identified as Asian, Pacific Islander, American Indian or Alaska Native]	Age, sex, race/ethnicity, DM,,CKD, coronary atherosclerosis and other heart disease,, cardiomyopathy, cardiovascular disease including hypertension, cancer, COPD, HIV, chronic liver disease, cirrhosis, and alcohol dependency

#: number, HTN: hypertension, DM: diabetes mellitus, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease, CHF: congestive heart failure, HIV: human immunodeficiency virus.

COVID-19 Severity

The severity of COVID-19 in patients with G6PD deficiency varied across studies, highlighting both differences and similarities in clinical outcomes when compared to the control groups. These studies collectively indicate that while G6PD deficiency may not universally predict increased severity in all aspects of COVID-19, there are specific parameters and subgroups in which the deficiency significantly impacts outcomes.

In Mushtaq et al. (2022), there was no significant difference between the study group (patients with COVID-19 infection and G6PD deficiency) and the control group (patients with normal G6PD activity) regarding the need for blood transfusions, assisted ventilation, ICU admission, duration of hospitalization, or occurrence of thrombotic events or death during their hospital stay. This suggests that G6PD deficiency may not significantly influence specific severity outcomes in COVID-19 patients.

Parnasa et al. (2023) presented a more detailed comparison, showing several significant differences between the study group and the control group. The maximal C-reactive protein levels were slightly higher in the control group (11.1 ± 11.0) than in the study group (10.1 ± 8.6), with a p-value of 0.029, indicating statistical significance. Mortality rates were insignificant, with 7 deaths in the study group compared to 421 in the control group ($p = 0.1$). However, ICU admissions and critical illness were significantly higher in the control group ($n = 489$) than in the study group ($p = 0.003$). The prevalence of comorbid conditions, such as heart disease, lung disease, renal disease, liver disease, malignant disease, and hypertension did not show significant differences between the groups. However, diabetes mellitus was significantly more common in the control group ($n = 817$) than in the study group (15), with a p-value of 0.035.

Youssef et al. (2021) identified several key indicators of increased severity in patients with G6PD deficiency compared with those with normal G6PD levels. G6PD levels were significantly lower in the G6PD deficient group (5.6) than in the control group (12.2), with a p-value of 0.0002. The PaO2/FiO2 ratio, an important marker of respiratory function, was also significantly lower in the G6PD deficient group (108) than in the control group (159) ($p = 0.05$). Furthermore, the G6PD deficient group required significantly more days on mechanical ventilation (21 days) than the control group (10.25 days), with a p-value of 0.04.

Kumar et al. (2021) provided another perspective on COVID-19 severity, showing no significant differences between the study and control groups in terms of initial oxygenation status upon admission. Most patients were admitted to room air, with 88.6% in the study group and 87.9% in the control group ($p = 0.75$). Oxygen support was required by 11.4% of the study group and 11.4% of the control group ($p = 0.99$). Non-invasive ventilation (NIV) and mechanical ventilation were rarely required in either group, with no significant differences.

Elsea et al. (2023) highlighted racial disparities in COVID-19 severity among veterans with G6PD deficiency. Black male veterans under 65 years with G6PD deficiency had a 1.5-fold increased likelihood of severe outcomes from SARS-CoV-2 infection compared to those without G6PD deficiency (OR, 1.47; 95% CI, 1.03-2.09). This increased risk was even more pronounced among White male veterans with G6PD deficiency, who had a 3.6-fold increased likelihood of severe outcomes compared to their non-deficient counterparts aged 65 years or older (OR, 3.58; 95% CI, 1.64-7.80).

Liver and Kidney Function Tests

The studies, liver function tests revealed varying effects on patients with G6PD deficiency and COVID-19. Alotaibi et al. (2023) highlighted elevated AST, ALT, and bilirubin levels in G6PD and COVID-19 patients compared to those with COVID-19 alone. Mushtaq et al. (2022) noted differences in bilirubin levels between COVID-19 positive and negative groups with and without G6PD deficiency. Youssef et al. (2021) reported elevated AST, ALT, ALP, and bilirubin levels in a study group compared to controls, indicating liver impairment in G6PD deficient patients with COVID-19. Al-lehebe et al. (2022) found significantly higher ALP levels in COVID-19 patients with G6PD deficiency compared to those without deficiency and healthy controls. Kumar et al. (2021) observed elevated ALT levels and lower creatinine more frequently in COVID-19 patients without G6PD deficiency than in the control group. These findings underscore the complex interplay between G6PD deficiency and liver health during COVID-19. In-depth data on Liver and Kidney Function Tests for included studies found in table 3 and (supplement 4).

Table 3: liver function tests and kidney function tests.

Study ID/REF	**(1) Alotaibi et al. (2023)**			**(2) Mushtaq et al.(2022)**				**(3) Parnasa et al.(2023)**	**(4) Youssef et al.(2021)**		**(5) Al-lehebe et al.(2022)**			**(6) Israel et al.(2023)**	**(7) Kumar et al.(2021)**		**(8) Elsea et al.(2023)**
	G6PDd+ COVID-19 group	**G6PDd group**	**COVID-19 group**	**COVID-19+ G6PDd group**	**COVID-19 group**	**G6PDd group**	**Healthy controls group**	**N/A**	**COVID-19 + G6PDd group**	**COVID-19 group**	**COVID-19 + G6PDd group**	**COVID-19 group**	**Healthy controls group**	**N/A**	**COVID-19 + G6PDd group**	COVID-19 group	N/A
AST mean ± SD/SE or median (range)	39.56 SD: 34.75	32.56 SD:36.23	31.29 SD:37.12	N/A	N/A	N/A	N/A	N/A	176 (18-302)	134 (32-350)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ALT mean ± SD/SE or median (range)	34.21 SD: 34.39	29.69 SD: 44.28	28.99 SD: 40.01	N/A	N/A	N/A	N/A	N/A	* 216 (35-503)	* 148 (22-527)	N/A	N/A	N/A	N/A	NA	NA	N/A
ALP mean ± SD/SE or median (range)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	131 (58-279)	167 (65-449)	120.253 SE:6.234	81.515 SE:5.910	61.050 SE:12.730	N/A	N/A	N/A	N/A
PT mean ± SD/SE or median (range)	11.43 SD: 1.31	11.55 SD:1.25	11.47 SD: 3.56	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PTT mean ± SD/SE or median (range)	26.35 SD: 2.08	27.73 SD: 3.26	28.31 SD: 4.55	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fibrinogen mean ± SD/SE or median (range)	3.33 SD:1.92	3.26 SD: 1.39	4.49 SD: 1.98	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Albumin mean ± SD/SE or median (range)	37.85 SD: 6.28	42.43 SD: 4.60	40.68 SD: 5.10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bilirubin mean ± SD/SE or median (range)	21.94 SD: 23.63	27.51 SD:36.26	21.94 SD: 23.6	18.19 SE:2.63	17.9 SE:1.18	20.95 SE:1.46	12.5 SE:0.30	N/A	2.0 (0.5-2.3)	1.6 (0.5-3.8)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
creatinin mean ± SD/SE or median (range)	74.67 SD: 69.34	63.94 SD: 60.16	125.61 SD:175.73	N/A	N/A	N/A	N/A	N/A	# 2.0 (0.86-6.4)	# 3.3 (0.7-17)	N/A	N/A	N/A	N/A	NA	NA	N/A
BUN mean ± SD/SE or median (range)	6.17 SD: 8.65	4.27 SD: 3.24	5.71 SD: 4.01	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

** Elevated ALT (> 40U/L), # Elevated creatinine.*

CBC

The Complete Blood Count (CBC) results across the studies provided various insights into the differences among the groups. In Mushtaq et al.(2022), COVID-19 positive patients with G6PD deficiency showed mean white blood cell (WBC) counts of 6.56, hemoglobin (Hb) levels of 13.37 g/dL, and hematocrit (Hct) percentages of 40.63%. These values compared to COVID-19 positive patients with normal G6PD activity who had slightly higher WBC counts (8.7), similar Hb levels (13.59 g/dL), and slightly lower Hct percentages (40.26%).

For COVID-19 negative patients with G6PD deficiency, WBC counts averaged 7.05, Hb levels were 13.26 g/dL, and Hct percentages were 40.97%. In contrast, COVID-19 negative patients with normal G6PD activity had WBC counts of 6.72, higher Hb levels (14.9 g/dL), and Hct percentages (43.5%).

In Youssef et al.(2021), the study group had median WBC counts of 5.0 (range 3.0–8.3), Hb levels of 8.1 (range, 6.6–11), and Hct percentages of 26% (range 22–34). The control group showed similar patterns, with a median WBC count of 5.2 (range 2.1–6.9), Hb level of 10 (range, 6.5–13), and Hct percentage of 32% (range, 20–40).

Al-lehebe et al.(2022) focused on patients with COVID-19 and G6PD deficiency reported mean WBC counts of 5.735 ± 0.702, Hb levels of 11.869 ± 0.9574 g/dL, and packed cell volume (PCV) of 35.609 ± 1.892. For COVID-19 patients without G6PD deficiency, the mean WBC count was 6.802 ± 1.023, Hb level was 13.388 ± 0.581 g/dL, and PCV was 40.164 ± 1.723. Healthy controls had higher Hb levels (15.620 ± 0.859 g/dL) and PCV (46.862 ± 2.067).

In-depth data on CBC parameters for the studies included are shown in Table 4 and (Supplement 4).

Table 4: complete blood count.

Study ID/REF	(1) Alotaibi et al. (2023)			(2) Mushtaq et al.(2022)				(3) Parnasa et al.(2023)	(4) Youssef et al.(2021)		(5) Al-lehebe et al.(2022)			(6) Israel et al.(2023)	(7) Kumar et al.(2021)		(8) Elsea et al.(2023)
	G6PD+COVID-19 group	G6PD group	COVID-19 group	COVID-19 + G6PDd group	COVID-19 group	G6Pdd group	Healthy controls group	N/A	COVID-19 + G6PDd group	COVID-19 group	: COVID-19 + G6PDd group	COVID-19 group	Healthy controls group	N/A	COVID-19 + G6PDd group	COVID-19 group	N/A
#White Blood Cells (WBC) x 10^9/L mean ± SD/SE or median(range)	N/A	N/A	N/A	6.56 SE:0.47	8.7 SE:0.29	7.05 SE:0.18	6.72 SE:0.14	N/A	5. 1 (3.0–8.3)	5.2 (2.1–6.9)	5.735 SE:0.702	6.802 SE:1.023	6.364 SE:1.009	N/A	N/A	N/A	N/A
#Hemoglobin (Hb) g/ mean ± SD/SE or median(range)	N/A	N/A	N/A	13.37 SE:0.32	13.59 SE:0.15	13.26 SE:0.13	14.9 SE: 0.09	N/A	8.1 (6.6–11)	10 (6.5–13)	11.869 SE:0.9574	13.388 SE:0.581	15.620 SE:0.859	N/A	N/A	N/A	N/A
#Hematocrit (Hct mean ± SD/SE or median(range)	N/A	N/A	N/A	40.63 SE:0.77	40.26 SE:0.43	40.97 SE:0.46	43.5 SE:0.33	N/A	26 (22–34)	32 (20–40)	35.609 1.892SE:	40.164 1.723SE:	46.862 2.067SE:	N/A	N/A	N/A	N/A
#Mean Corpuscular	N/A	N/A	N/A	87.88	85.67	86.20	83.61 SE:0.39	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Volume (MCV) Fl mean ± SD/SE or median(range)				SE:1.26	SE:0.31	SE:0.79											
#Platelets (PLT) x 10^9/ mean ± SD/SE or median(range)	N/A	N/A	N/A	277.12 SE:14.69	277.50 SE:6.42	263.68 SE:8.94	247.70 SE:4.44	N/A	405 (179–571)	425 (337–626)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
#Absolute Neutrophil Count (ANC) mean ± SD/SE or median(range)	N/A	N/A	N/A	3.77 x 10^9/L SE:0.47	5.07 x 10^9/L SE:0.28	4.15 x 10^9/L SE:0.16	3.16 x 10^9/L SE:0.14	N/A	# 62 (47–82)	# 60 (35–74)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
#Lymphocyte Count (Lym#) x 10^9/L mean ± SD/SE or median(range)	N/A	N/A	N/A	2.05 SE:0.11	2.20 SE:0.05	2.5 SE:0.08	4.0 SE:0.12	N/A	393 (111–738)	618 (191–1917)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
#Monocyte Count (Mon#) x 10^9/L mean ± SD/SE or median(range)	N/A	N/A	N/A	0.56 SE:0.05	0.76 SE:0.03	0.64 SE:0.05	0.60 SE:0.03	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
#Eosinophil Count x 10^9/L mean ± SD/SE or median(range)	N/A	N/A	N/A	0.17 SE:0.02	0.5 SE:0.03	0.20 SE:0.02	0.19 SE:0.01	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

#Basophil Count (Bas#) x 10^9/L mean ± SD/SE or median(range)	N/A	N/A	N/A	0.04 SE:0.00	0.05 SE:0.00	0.05 SE:0.01	0.14 SE:0.01	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

**lowest values, # percent (%).*

HB levels in patients with COVID-19 vs those with COVID-19 and G6PD deficiency.

This meta-analysis compared hemoglobin (HB) levels between COVID-19 patients and individuals with both G6PD deficiency and COVID-19. The overall mean difference (MD) using a random-effects model was 1.0291, with 95% confidence intervals (CI) of [0.1176 and 1.9407], indicating a statistically significant difference (z = 2.21, p = 0.0269) in HB levels between the two groups (Figure 2). Significant heterogeneity was present among the studies (I^2 = 81.9%, p = 0.0039), indicating a substantial variation in effect sizes. Overall, the analysis suggests a significant difference in hemoglobin levels between the COVID-19 and G6PD and COVID-19 groups, but the high heterogeneity warrants caution in interpreting the results.

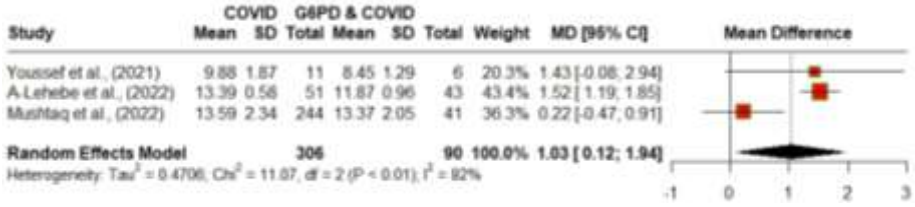

Figure 2: presents forest plot of the mean difference of HB level across patients with COVID vs COVID and G6PD.

HCT level in patients with COVID-19 vs patients with COVID-19 and G6PD

A meta-analysis comparing hematocrit (HCT) levels between COVID-19 patients and individuals with both G6PD deficiency and COVID-19. The random-effects model showed an MD of 1.3205 with a 95% confidence interval (CI) of [-2.8509 to 5.4919], which was statistically insignificant (z = 0.62, p = 0.5350) **(**Figure 3). Moderate heterogeneity was detected (I^2 = 69.2%, p = 0.0715) and the p-value for heterogeneity was significant.

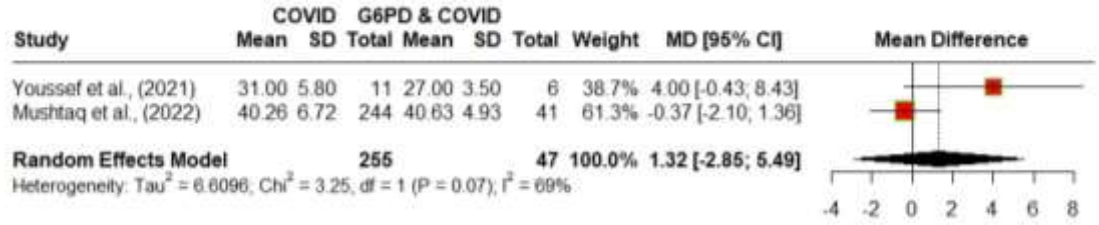

Figure 3: Presents forest plot of the mean difference of HCT level across patients with COVID vs COVID and G6PD.

WBC level in patients with COVID-19 vs patients with COVID-19 and G6PD

A meta-analysis comparing WBC counts between COVID-19 patients and those with both G6PD deficiency and COVID-19. The random-effects model showed a statistically significant MD of 1.39 with a 95% CI of [0.16, 2.62] (Figure 4). The heterogeneity was low and insignificant (I^2 = 23.2%, p = 0.2722).

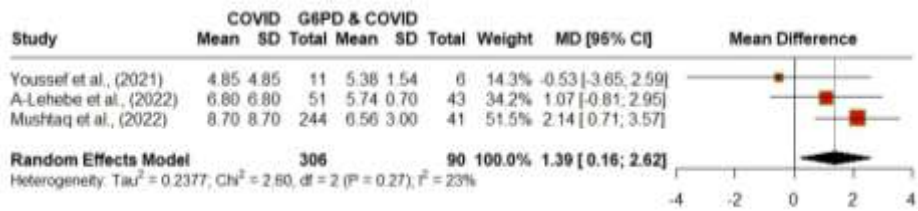

Figure 4: Presents a forest plot of the mean difference of WBC counts across patients with COVID vs COVID and G6PD.

Other lab tests

Analysis of other laboratory results highlighted several key differences among the study groups. Alotaibi et al. reported that COVID-19 patients with G6PD deficiency exhibited elevated levels of CRP, ferritin, LDH, and D-dimer compared to those with normal G6PD activity. The levels of inflammatory markers were generally higher in the COVID-19 group than in the G6PD group.

In Youssef et al., the study group showed significantly higher levels of lactate, IL-6, CRP, ferritin, LDH, D-dimer, glucose, and triglycerides than the control group, indicating a heightened inflammatory response and metabolic disturbance.

Al-lehebe et al. revealed that COVID-19 patients with G6PD deficiency had higher ferritin and LDH levels compared to those without G6PD deficiency and healthy controls. GOT and GLP levels were also elevated in the patient groups compared with the healthy controls. In-depth data on these tests for the included studies are presented in Table 5 and (Supplement 4).

Table 5: other lab tests.

Study ID/REF	**Alotaibi et al. (2023)[27]**			**Mushtaq et al.(2022)[28]**				**Parnasa et al.(2023)[29]**	**Youssef et al.(2021)[30]**		**Al-lehebe et al.(2022)[31]**			**Israel et al.(2023)[32]**	**Kumar et al.(2021)[33]**		**Elsea et al.(2023)[34]**
	G6PD+ COVID-19 group	G6PD group	COVID-19 group	COVID-19 + G6PDd group	COVID-19 group	G6PDd group	Healthy controls group	N/A	COVID-19 + G6PDd group	COVID19 group	COVID-19 + G6PDd group	COVID-19 group	Healthy controls group	N/A	COVID-19 + G6PDd group	COVID-19 group	N/A
Lactate, mmol/L mean ± SD/SE or median(range)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	5.0 (1.3-16)	2.1 (1.2-3.5)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
IL-6, pg/L mean ± SD/SE or median(range)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	278 (57-669)	577 (5-2957)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CRP, mg/L mean ± SD/SE or median(range)	25.32 SD: 50.47	35.71 SD: 53.97	50.39 SD: 78.75	N/A	N/A	N/A	N/A	N/A	28 (15-51)	21 (0.87-41)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ferritin, mg/L mean ± SD/SE or median(range)	1977.11 SD:4570.85	565.91 SD:1811.98	545.53 SD:1660.98	N/A	N/A	N/A	N/A	N/A	7095 (916-32,659)	1371 (476-3648)	226.44 SE: 11.232	190.31 SE: 11.54	83.38 SE: 5.406	N/A	N/A	N/A	N/A
LDH, IU/L mean ± SD/SE	614.77 SD: 516.32	466.07 SD:462.34	321.70 SD: 221.56	N/A	N/A	N/A	N/A	N/A	663 (378-996)	518 (208-862)	181.02	150.08 SE12.776	114.65	N/A	N/A	N/A	N/A

or median(range)											SE: 11.60		SE: 6.765				
D-dimer mean ± SD/SE or median(range)	2.95 SD: 3.52	2.07 SD:2.46	1.92 SD:3.66	N/A	N/A	N/A	N/A	N/A	13 (0.6-20)	5.7 (0.41-20)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Glucose, mg/dl mean ± SD/SE or median(range)	6.08 SD: 2.63	5.46 SD:2.49	6.16 SD: 2.78	N/A	N/A	N/A	N/A	N/A	* 242 (133-378)	* 209 (91-310)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Triglyceride, mg/dl mean ± SD/SE or median(range)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	218 (65-416) #	193 (85-543) #	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Troponin-1, ng/ml mean ± SD/SE or median(range)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.28 (0.006-0.5)	0.85 (0.006-6.8)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
GOT mean ± SD/SE or median(range)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	37.81 SE: 0.460	36.71 SE: 0.707	36.85 SE: 1.034	N/A	N/A	N/A	N/A
GLP mean ± SD/SE or median(range)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	36.28 SE: 0.846	36.04 SE: 0.640	34.60 SE: 7.344	N/A	N/A	N/A	N/A
Highest QTc on EKG, ms	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	486 (446-528)	476 (437-551)	N/A	N/A	N/A	N/A	N/A	N/A	N/A

**Highest glucose, # Highest triglyceride.*

LDH level in patients with COVID-19 vs patients with COVID-19 and G6PD

A meta-analysis comparing lactate dehydrogenase (LDH) levels between COVID-19 patients and individuals with both G6PD deficiency and COVID-19. The random-effects model yielded an MD of -107.60 with a 95% CI of [-244.72; 29.51], which was not statistically significant (z = -1.54, p = 0.1240) (Figure 5). Significant heterogeneity was detected (I^2 = 59.6%, p = 0.0841), suggesting some variability across studies.

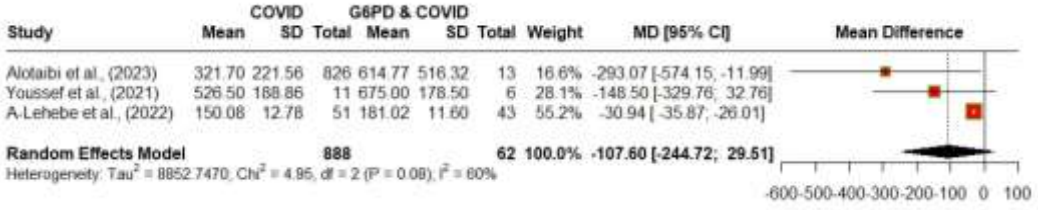

Figure 5: presents a forest plot of the mean difference of LDH level across patients with COVID vs COVID and G6PD.

Ferritin level in patients with COVID-19 vs patients with COVID-19 and G6PD

A meta-analysis comparing ferritin levels in COVID-19 patients and those with both G6PD deficiency and COVID-19 revealed an insignificant pooled MD of approximately -2529.78 (95% CI: -7092.01–2032.45, z = -1.09, p = 0.2771). Heterogeneity was significant, and a random-effects model was used for the meta-analysis (Figure 6).

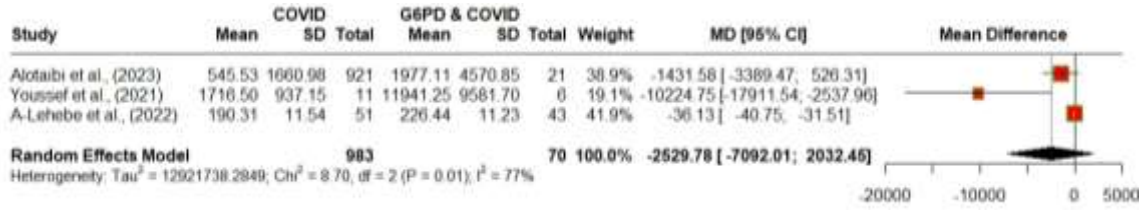

Figure 6: Presents a forest plot of the mean difference of ferritin levels across patients with COVID vs COVID and G6PD.

Discussion

COVID-19 affects a wide spectrum of individuals, with varying degrees of severity across different populations. Reports have consistently indicated that certain vulnerable groups experience more severe outcomes.[35,36] This study focused on a specific subset of the population: individuals with G6PD deficiency. By examining the impact of COVID-19 on those with G6PD deficiency, we aimed to uncover the unique vulnerabilities and clinical characteristics within this group, contributing to a more subtle understanding of disease severity and informing targeted management strategies. Based on the currently available information, our study is the first comprehensive systematic review acknowledging COVID-19 severity and associated laboratory test abnormalities in G6PD deficient patients compared to controls.

The WHO criteria for assessing respiratory conditions, such as Acute Respiratory Distress Syndrome (ARDS) and severe COVID-19, include several key parameters that are crucial for determining the severity of the illness and guiding treatment decisions. One critical measure is SpO2 (Oxygen Saturation), which indicates the percentage of oxygen-saturated hemoglobin in the blood; a value below 94% on room air signifies severe illness.[37] Additionally, the PaO2/FiO2 ratio, which represents the ratio of arterial oxygen partial pressure to fractional inspired oxygen, was used to assess hypoxemia severity, with a ratio below 300 mm Hg indicating a severe condition.[38,39] The respiratory rate is another important factor, as a rate exceeding 30 breaths per minute is a critical indicator of respiratory distress. Furthermore, lung infiltrates in greater than 50% of the imaging studies have highlighted significant lung involvement. These criteria are vital for healthcare providers to evaluate the severity of respiratory conditions and to make informed treatment decisions.[37,40]Some included studies considered different parameters (e.g., ICU admission, hospital admission, mechanical ventilation, inflammatory markers) for assessing the severity

The PaO2/FiO2 ratio is one of several factors indicating the severity of COVID-19 and classifies the severity of ARDS according to WHO criteria.[41] This ratio often decreases in COVID-19 patients due to complex and multifactorial reasons, indicating significant impairment in pulmonary gas exchange.[39,42]

The relationship between G6PD deficiency and COVID-19 severity remains complex and context-dependent, as evidenced by varying findings across studies. While Mushtaq et al. (2022) found no significant differences in key severity parameters (e.g., ICU admission, mortality) between G6PD-deficient and control groups, Parnasa et al. (2023) reported higher ICU admissions and critical illness in controls, alongside lower C-reactive protein levels in G6PD-deficient patients. Conversely, Youssef et al. (2021) identified G6PD deficiency as a risk factor for worse respiratory outcomes, with lower PaO2/FiO2 ratios and prolonged mechanical ventilation. Kumar et al. (2021) observed no significant differences in oxygenation needs, suggesting G6PD deficiency may not universally exacerbate COVID-19 severity. However, Elsea et al. (2023) highlighted racial and age disparities, with G6PD-deficient Black and White male veterans showing elevated risks of severe outcomes. These divergent findings underscore the influence of demographic, clinical, and methodological variables on COVID-19 outcomes in G6PD-deficient populations. Further research is needed to clarify the mechanisms by which G6PD deficiency modulates disease severity and to identify high-risk subgroups for targeted interventions.

Recent findings reveal that 2-11% of COVID-19 patients have chronic liver disease. During the SARS outbreak, liver damage affected approximately 60% of patients.[43,44] Currently, hepatic dysfunction is noted in 14-53% of COVID-19 cases, particularly in those with severe symptoms. Acute liver injury with elevated liver enzymes (AST and ALT) is predominantly observed in severe and critical cases of COVID-19 and is often correlated with poorer outcomes.[45] Liver involvement in COVID-19 may result from the direct cytopathic effects of the virus on liver cells, an excessive immune response, sepsis, or drug-induced liver injury.[44] Mild to severe renal impairment was seen in patients affected by COVID-19.[46] In our study, the impact of COVID-19 on liver and kidney function, particularly in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, underscores a multifaceted interaction between viral infection and metabolic vulnerability. Studies reveal consistent elevations in liver enzymes (AST, ALT, ALP) and bilirubin levels in G6PD-deficient COVID-19 patients, suggesting exacerbated hepatic injury compared to non-deficient individuals (Alotaibi et al., 2023; Youssef et al., 2021). This phenomenon may be attributed to the heightened oxidative stress caused by G6PD deficiency, compounded by the inflammatory and cytotoxic effects of SARS-CoV-2, which collectively impair hepatocyte function. Al-lehebe et al. (2022) further emphasize this by reporting significantly higher ALP levels in G6PD-deficient COVID-19 patients, indicating potential cholestatic injury or bile duct dysfunction. Conversely, Kumar et al. (2021) observed elevated ALT levels and lower creatinine in COVID-19 patients without G6PD deficiency, suggesting differential renal and hepatic responses between groups. These findings highlight the unique susceptibility of G6PD-deficient individuals to COVID-19-induced organ damage, necessitating tailored clinical monitoring and management. The interplay between G6PD deficiency and COVID-19 also raises questions about the role of oxidative stress in multi-organ dysfunction, warranting further investigation into therapeutic strategies targeting redox balance. Overall, these studies underscore the importance of considering genetic predispositions, such as G6PD deficiency, in understanding and managing COVID-19 complications.

Several hematological parameters, such as platelet count, total white blood cell (WBC) count, lymphocyte count, neutrophil count, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and hemoglobin levels, have been associated with COVID-19 infection and its severity.[47] Studies conducted in China and other countries have highlighted the crucial role of these hematological markers in understanding disease progression.[48] Common laboratory abnormalities in COVID-19 patients include decreased WBC and lymphocyte counts, reduced hemoglobin levels, neutrophilia, and thrombocytopenia. These changes, particularly in the WBC and lymphocyte counts, may be explained by virus-induced apoptosis.[49] Our analysis reveals that COVID-19 patients with G6PD deficiency exhibit lower WBC counts, lymphocytes, and hemoglobin levels compared to those with normal G6PD activity.[50-52]Understanding these hematological changes is crucial for the follow-up and management of COVID-19 patients, particularly those with G6PD deficiency. Comprehensive WBC count and differential analysis can help identify the predictors of disease prognosis. This thorough assessment provides a strong foundation for comparing the severity of COVID-19 in G6PD-deficient patients with that in controls.

The analysis of Complete Blood Count (CBC) parameters across studies reveals significant hematological differences between COVID-19 patients with and without glucose-6-phosphate dehydrogenase (G6PD) deficiency, highlighting the interplay between genetic predisposition and viral infection. Mushtaq et al. (2022) reported lower mean white blood cell (WBC) counts (6.56) in G6PD-deficient COVID-19 patients compared to those with normal G6PD activity (8.7), suggesting a potential blunted immune response in G6PD-deficient individuals. Hemoglobin (Hb) levels were relatively stable across COVID-19-positive groups, but COVID-19-negative patients with normal G6PD activity exhibited higher Hb (14.9 g/dL) and hematocrit (Hct) levels (43.5%) compared to G6PD-deficient counterparts, indicating a protective effect of normal G6PD activity against anemia. Youssef et al. (2021) further emphasized this trend, with G6PD-deficient COVID-19 patients showing markedly lower median Hb (8.1 g/dL) and Hct (26%) levels compared to controls, underscoring the exacerbation of anemia in this population. Al-lehebe et al. (2022) corroborated these findings, reporting significantly lower Hb (11.869 g/dL) and packed cell volume (PCV) (35.609%) in G6PD-deficient COVID-19 patients, suggesting impaired erythropoiesis and oxygen transport.

Meta-analyses reinforced these observations. A significant mean difference (MD = 1.0291, p = 0.0269) in Hb levels between COVID-19 patients with and without G6PD deficiency highlights the vulnerability of G6PD-deficient

individuals to anemia, though high heterogeneity (I^2 = 81.9%) necessitates cautious interpretation. Conversely, Hct levels showed no significant difference (MD = 1.3205, p = 0.5350), indicating variable effects of G6PD deficiency on hematological parameters. WBC counts demonstrated a significant difference (MD = 1.39, $p < 0.05$), with lower counts in G6PD-deficient patients, potentially reflecting impaired immune mobilization. These findings underscore the need for tailored clinical monitoring and interventions to address hematological disparities in G6PD-deficient COVID-19 patients, emphasizing the complex interaction between genetic factors and viral infection.

Previous studies showed the importance of some inflammatory markers as a predictors for COVID-19 severity and ICU admissions.[53] In our study, the analysis of laboratory markers in COVID-19 patients with and without G6PD deficiency reveals significant differences in inflammatory and metabolic responses, underscoring the interplay between genetic predisposition and viral infection. Alotaibi et al. reported elevated levels of CRP, ferritin, LDH, and D-dimer in G6PD-deficient COVID-19 patients compared to those with normal G6PD activity, suggesting a heightened inflammatory state and potential tissue damage. Similarly, Youssef et al. found significantly higher levels of lactate, IL-6, CRP, ferritin, LDH, D-dimer, glucose, and triglycerides in G6PD-deficient COVID-19 patients, indicating a robust inflammatory response and metabolic dysregulation. Al-lehebe et al. further corroborated these findings, demonstrating elevated ferritin, LDH, GOT, and GLP levels in G6PD-deficient COVID-19 patients compared to non-deficient individuals and healthy controls, highlighting liver involvement and cellular injury.

Meta-analyses provided additional insights. While LDH levels showed no significant difference between COVID-19 patients with and without G6PD deficiency (MD = -107.60, p = 0.1240), the significant heterogeneity (I^2 = 59.6%) suggests variability across studies, potentially due to differences in disease severity or patient demographics. Similarly, ferritin levels did not significantly differ between groups (MD = -2529.78, p = 0.2771), though the high heterogeneity underscores the complexity of ferritin as an acute-phase reactant. These findings collectively emphasize the exacerbated inflammatory and metabolic disturbances in G6PD-deficient COVID-19 patients, necessitating tailored monitoring and therapeutic strategies to mitigate organ dysfunction and improve outcomes.

From a pathophysiological perspective, G6PD plays a crucial role in defense against oxidative stress by facilitating the regeneration of glutathione, a vital antioxidant. Glutathione boosts both innate and adaptive immunity, which means protecting against bacterial and viral infections.[48,54] G6PD converts glucose-6-phosphate into 6-phosphogluconolactone, generating reduced nicotinamide adenine dinucleotide phosphate (NADPH), which is essential for lowering glutathione disulfide (GSSG) to its active form, glutathione (GSH). GSH scavenges reactive oxygen species (ROS) and other free radicals, thereby easing oxidative damage. In G6PD deficiency, the antioxidative capacity is damaged, making individuals more exposed to oxidative stress and infections.[50,55] SARS-CoV-2, the virus responsible for COVID-19, aggravates oxidative stress by disrupting the balance of the antioxidant system, which has already deteriorated due to G6PD deficiency. This leads to increased viral replication and infection severity, as both G6PD deficiency and COVID-19 deteriorate the antioxidant system through similar pathways, rendering individuals with G6PD deficiency particularly vulnerable to severe outcomes.[49,56] Additionally, immune inflammation in airway epithelial cells during infection can induce G6PD activity, increasing the production of glutathione, ROS, nitrotyrosine, and NADPH oxidase 2 (NOX2). However, in G6PD deficiency, this adaptive response is inhibited, further contributing to the severity of COVID-19 and associated lab test abnormalities.[52]

Strengths and limitations

The strengths of our study come from the fact that it is the first comprehensive systematic review to provide a robust analysis of COVID-19 severity, liver/kidney function, and hematological parameters in patients with G6PD deficiency, offering valuable insights into the interplay between genetic predisposition and viral infection. Key strengths include the inclusion of diverse populations, detailed comparisons of clinical and laboratory outcomes, and meta-analyses that identify trends across studies, providing nuanced insights into subgroup vulnerabilities. Additionally, the meta-analyses on Hb, HCT, and WBC levels offer a quantitative synthesis of findings, enhancing the reliability of conclusions.

In our systematic review, several limitations are evident. First, the review consists of both cohort and case-control studies, which introduces variability in study design and complicates the comparison of findings. Second, selection bias, recall bias, and uncontrolled confounding variables are potential issues, particularly in case-control studies. Third, methodological quality varies, affecting the strength of conclusions. Fourth, differences in outcome definitions and measurements prevent data pooling, and findings may not be generalizable due to demographic and regional differences. Fourth, Inconsistent findings, such as the lack of significant differences in LDH and ferritin levels, could be due to confounding factors like disease severity, comorbidities, or methodological differences. Finally, small number and high heterogeneity of the included studies which may stem from variability in study designs, sample sizes, and patient demographics. While we provided some insight into the sources of variability, the observed heterogeneity underscores the need for caution when interpreting the pooled estimates.

Clinical implications and recommendations

The findings indicate that G6PD deficiency may exacerbate specific aspects of COVID-19, such as respiratory dysfunction (lower PaO2/FiO2 ratios), anemia (lower Hb levels), and liver impairment (elevated AST, ALT, ALP). Clinicians should monitor G6PD-deficient patients for these complications, particularly in high-risk subgroups like Black and White male veterans, who showed increased severity in Elsea et al. (2023). Elevated inflammatory markers (CRP, ferritin, LDH) in G6PD-deficient patients suggest a heightened inflammatory response, warranting close monitoring and potential anti-inflammatory interventions. These highlight the need for increased attentiveness and personalized management strategies for patients with G6PD deficiency. This also emphasizes the importance of considering G6PD status when assessing and managing COVID-19 severity. However, the high heterogeneity in meta-analyses calls for cautious interpretation and highlights the need for standardized, large-scale studies to clarify the role of G6PD deficiency in COVID-19 outcomes. Clinically, tailored management strategies, including regular CBC, liver function tests, and respiratory support, are recommended for G6PD-deficient COVID-19 patients to mitigate adverse outcomes. Additionally, addressing racial disparities and comorbidities, such as diabetes mellitus, should be prioritized in clinical care and future research to optimize patient outcomes.

Conclusion

In conclusion, this study highlights the vital role of laboratory tests in understanding COVID-19 severity, especially in those with G6PD deficiency. Our detailed analysis shows that patients with G6PD deficiency have lower white blood cell counts, lymphocyte counts, and hemoglobin levels than those without the deficiency. We also found that G6PD-deficient patients had a lower PaO2/FiO2 ratio and needed more days on mechanical ventilation. This suggests that G6PD deficiency makes individuals more susceptible to severe COVID-19 outcomes. However, regarding liver enzymes(AST/ALT), there have been conflicting results between G6PD-deficient patients and controls, indicating that further research is needed to fully understand how the virus affects them. These findings are crucial for the care and follow-up of COVID-19 patients with G6PD deficiency. By identifying laboratory tests that predict disease outcomes, healthcare providers can create more effective management plans to help this vulnerable group. Our study lays the groundwork for future research and adds to the growing understanding of how G6PD deficiency affects COVID-19 severity.

Disclosure

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