Glucose-6-Phosphate Dehydrogenase Deficiency and COVID-19 Mortality, Intensive Care Unit Admission, and Length of Hospitalization

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ABSTRACT **Background:** The coronavirus disease 2019 (COVID-19) pandemic has severe consequences in terms of mortality and morbidity. Knowledge of factors that impact COVID-19 may be useful in the search for treatments.

Objectives: To determine the effect of glucose-6-phosphate dehydrogenase (G6PD) deficiency on morbidly and mortality associated with COVID-19.

Methods: All patients admitted to the Hadassah Hebrew University Medical Center between 01 March 2020 and 03 May 2021 with a diagnosis of COVID-19 were included. We retrospectively retrieved demographic, clinical, and laboratory data from the hospital's electronic medical records. The main outcomes were mortality, intensive care unit (ICU) admission, and severity of COVID-19.

Results: The presence of G6PD deficiency emerged as an independent protective predictor for ICU admission (odds ratio [OR] 0.258, 95% confidence interval [95%CI] 0.077–0.619, $P = 0.003$) and the development of critical illness (OR 0.121, 95%CI 0.005–0.545, $P = 0.006$). Moreover, patients with G6PD deficiency had a trend toward lower mortality rates that did not reach statistical significance (OR 0.541, 95%CI 0.225–1.088, $P = 0.10$).

Conclusions: Patients with G6PD deficiency were less likely to have a severe disease, had lower rates of ICU admission, and trended toward lower mortality rates.

IMAJ 2023; 25: 88–90

KEY WORDS: coronavirus disease 2019 (COVID-19), glucose-6-phosphate dehydrogenase (G6PD), hospitalization, intensive care unit (ICU), mortality

Glucose-6-phosphate dehydrogenase (G6PD) deficiency (G6PD-D) is one of the most common genetic alterations [1] and is classified according to the level of the enzymatic activity. G6PD-D type 2 is common in the Middle East, and is specifically common among Kurdish Jews, where its prevalence reaches 70% [2]. Although an evolutionary rationale leads to the assumption that G6PD-D can harbor a protective effect against many kinds of infections, there is lack of data regarding the relationship between G6PD-D and the risk of severe viral infection in general and coronavirus disease 2019 (COVID-19) in particular. In this study, we evaluated the role of G6PD-D on COVID-19 in patient outcomes in one tertiary center in Israel.

PATIENTS AND METHODS

All patients admitted to the Hadassah Medical Center between 01 March 2020 and 03 May 2021 with a diagnosis of COVID-19 were included. We retrospectively retrieved demographic, clinical, and laboratory data from the hospital's electronic medical records. Information regarding the G6PD status was based on a standard allergy questionnaire taken at admission.

The main outcomes were mortality at the end of the analysis, intensive care unit (ICU) admission, severity of COVID-19 reported by the treating physician according to WHO criteria, and length of hospitalization. Chi-square test, Mann-Whitney test, and logistic regression were used to examine the associations between covariates and the main outcomes.

RESULTS

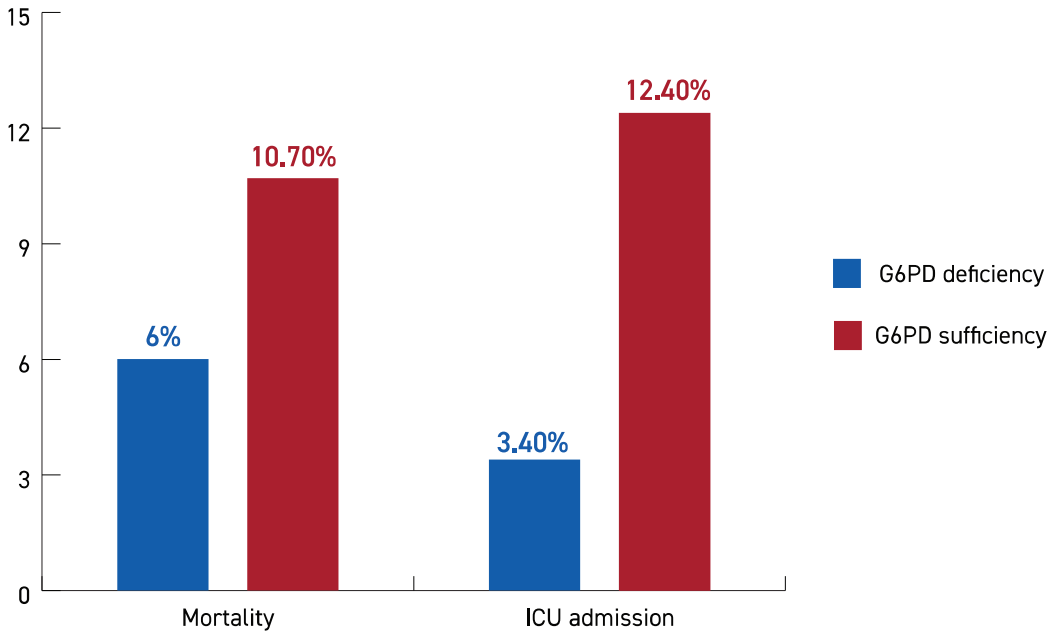
During the study period, 4046 patients were included, of whom 117 were declared to have G6PD-D. The main characteristics of patients and their outcomes are presented in Table 1. Except for a lower rate of diabetes mellitus among the G6PD-D group, the two groups did not differ in any other demographic or clinical parameters on admission. The presence of G6PD-D emerged as an independent protective predictor for ICU admission (odds ra-

Table 1. Patient characteristics and coronavirus disease 2019-related outcomes

	G6PD deficient, n=117 (2.9%)	G6PD sufficient, n=3929 (97.1%)	Odds ratio	95% confidence interval	*P*-value
Male sex, N (%)	66 (56.4%)	2038 (51.9%)			0.333
Age, year, mean	52.2 ± 20.0	52.8 ± 22.6			0.780
Co-morbidities					
Heart disease	19 (16.2%)	585 (14.9%)			0.686
Lung disease	7 (6%)	389 (9.9%)			0.160
Renal disease	11 (9.4%)	502 (12.8%)			0.280
Liver disease	3 (2.6%)	78 (2%)			0.660
Malignant disease	6 (5.1%)	278 (7.1%)			0.416
Diabetes mellitus	15 (12.8%)	817 (20.8%)			0.035
Hypertension	26 (22.2%)	1017 (25.9%)			0.362
Maximal C-reactive protein	10.1 ± 8.6	11.1 ± 11.0			0.029
Mortality	7 (6.0%)	421 (10.7%)	0.541	0.23–1.09	0.10
Intensive care unit admission	4 (3.4%)	489 (12.4%)	0.25	0.08–0.62	0.003
Severity (WHO criteria)					
Unspecified	22 (18.3%)	838 (21.3%)	0.81	0.482–1.302	0.38
Mild	55 (47.0%)	1638 (41.7%)	1	NA	NA
Moderate	18 (15.4%)	543 (13.8%)	1.027	0.589–1.71	0.935
Severe	22 (18.8%)	635 (16.2%)	1.062	0.635–1.72	0.821
Critical	0 (0.0%)	275 (7.0%)	0.121	0.005–0.545	0.0067
Duration of hospitalization (days)					
≤ 5	63 (53.85%)	2167 (55.15%)	NA	NA	1
6–9	31 (26.5%)	917 (23.34%)	1.17	0.74–1.79	0.49
10–19	21 (17.95%)	512 (13.09%)	1.41	0.84–30	0.17
20+	2 (1.71%)	333 (8.48%)	0.22	0.03–0.71	0.02

Figure 1. In-patient mortality and ICU admissions

G6PD = glucose-6-phosphate dehydrogenase, ICU = intensive care unit



tio [OR] 0.258, 95% confidence interval [95%CI] 0.077–0.619, $P = 0.003$) and the development of critical illness (OR 0.121, 95%CI 0.005–0.545, $P = 0.006$). Moreover, G6PD-D patients had a trend toward lower mortality rate that did not reach statistical significance (OR 0.541, 95%CI 0.225–1.088, $P = 0.10$). These results remained after adjustment for age, sex, and chronic diseases including hypertension, diabetes mellitus, liver disease, renal disease, lung disease, heart disease, and malignancy.

DISCUSSION

The results of this study demonstrate a surprisingly strong correlation between G6PD-D and the severity of COVID-19 among hospitalized patients and may imply causality. The biological mechanism, as well as the span of this correlation has still not been identified. It is unknown if a similar correlation can be found among other viral infections

Our trial has several limitations. First, as in any retrospective trial, errors in documentation are possible, as well as the presence of unmeasured confounders, although we have no reason to believe that such confounders exist. Second, the presence of G6PD-D was based on self-reporting, rather than by biochemical or genetic test. Third, our study included only one genetic variant of G6PD-D. It is unknown if these results are reproducible for other variants of G6PD-D.

CONCLUSIONS

The presumed protective effect of G6PD-D may help explain the pathophysiology of the deficiency, and this knowledge may be used to find a treatment for COVID-19 and other viral diseases.

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Kindness in ourselves is the honey that blunts the sting of unkindness in another.
Walter Savage Landor (1775–1864), English writer, poet, and activist

Capsule

Bivalent Omicron BA.1-adapted BNT162b2 booster in adults older than 55 years

In an ongoing phase 3 trial, adults older than 55 years who had previously received three 30 µg doses of the BNT162b2 vaccine were randomly assigned to receive 30 µg or 60 µg of BNT162b2, 30 µg or 60 µg of monovalent B.1.1.529 (omicron) BA.1-adapted BNT162b2 (monovalent BA.1), 30 µg (15 µg of BNT162b2+15 µg of monovalent BA.1), or 60 µg (30 µg of BNT162b2+30 µg of monovalent BA.1) of BA.1-adapted BNT162b2 (bivalent BA.1). **Winokur** and co-authors reported that 1846 participants underwent randomization. At 1 month after vaccination, bivalent BA.1 (30 µg and 60 µg) and monovalent BA.1 (60 µg) showed neutralizing activity against BA.1 superior to that of BNT162b2 (30 µg), with NT50 geometric mean ratios (GMRs) of 1.56 (95% confidence interval [95%CI] 1.17–2.08), 1.97 (95%CI 1.45–2.68), and 3.15 (95%CI 2.38–4.16), respectively. Bivalent BA.1 (both doses) and monovalent BA.1 (60 µg) were also noninferior to BNT162b2 (30 µg) with respect to seroresponse against BA.1. Between-group differences ranged from 10.9 to 29.1 percentage points. Bivalent BA.1 (either dose) was noninferior to BNT162b2 (30 µg) with respect to neutralizing activity against the ancestral strain, with NT50 GMRs of 0.99 (95%CI 0.82–1.20) and 1.30 (95%CI, 1.07–1.58), respectively. BA.4–BA.5 and BA.2.75 neutralizing titers were numerically higher with 30 µg bivalent BA.1 than with 30 µg BNT162b2. The safety profile of either dose of monovalent or bivalent BA.1 was similar to that of BNT162b2 (30 µg). Adverse events were more common in the 30 µg monovalent-BA.1 (8.5%) and 60 µg bivalent-BA.1 (10.4%) groups than in the other groups (3.6–6.6%).

N Engl J Med 2023; 388: 214
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