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Face masks and polycythemia is the standard hemoglobin cutoff valid in the pandemic?

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Abstract:

BACKGROUND: Polycythemia is a common reason for patients' admissions. With the introduction of COVID-19, face masks reached very common usage in the population. Masks may cause some degree of hypoxia that may result in high hemoglobin in healthy individuals. Here, we aimed to investigate the frequency of patients applying for high hemoglobin and tested for possible polycythemia vera (PV) in the pandemic era.

MATERIALS AND METHODS: We collected patients who applied to the hematology outpatient clinic between March 2019 and April 2021 for the study. The research was carried out at a single center at Ankara Oncology Training and Research Hospital. We collected demographic data such as age and sex, laboratory parameters such as complete blood count and erythropoietin level, concomitant diseases, smoking history, and spleen size.

RESULTS: The median age of the cohort was 41 (16–83). Groups were different regarding age (P = 0.04). Groups were similar regarding gender (P = 0.350). Comorbidities were similar in both groups. Smoking was more frequent in the pre-COVID era group (P = 0.046). The frequency of the Janus kinase 2 (JAK2) test order was 102 examinations out of 7920 for the pre-COVID era and 152 examinations out of 6087 for the COVID era; this was statistically significant (P < 0.001).

CONCLUSION: Clinicians may need to re-evaluate the threshold of hemoglobin levels to order JAK2 tests in the pandemic era, and the significance of mildly elevated hemoglobin may be neglected while testing for potential PV.

Keywords:

COVID-19, hemoglobin, Janus kinase mutation, myeloproliferative neoplasms, pandemic, polycythemia

Introduction

Polycythemia vera (PV) is a clonal myeloproliferative disease characterized by erythrocytosis and thrombocytosis, as well as leukocytosis, splenomegaly, thrombosis, microcirculatory symptoms, and the potential transformation to leukemia or myelofibrosis. Janus kinase 2 (JAK2) mutations are found in around 96% of people with PV.[1] In 2016, the WHO updated the diagnostic criteria as >16.5 gr/dl in men, >16.0 gr/dl in women or hematocrit >49% in men and >48% in women.[2]

In 2019, the first COVID-19 cases were identified in Wuhan in China, and in March 2020, the first case was identified in Turkey.[3] COVID-19 is considered to spread mostly from person to person, mostly through respiratory droplets created when an infected person coughs or sneezes.[4] For that reason, face masks carry vital importance in avoiding

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spreading.[5] People regularly were encouraged to use masks; however, the evidence is not strong, especially for outdoor use, its recommendation is explained based on the precautionary principle.[6] The Centers for Disease Control and Prevention (CDC) recommends using masks for older than 2 years of age in indoor public places; it is not generally advised for outdoor settings, but exceptions are in the areas with high cases and close activities with nonvaccinated population.[7] Face masks make it more difficult to breathe. Furthermore, each respiratory cycle involves the inhalation of an amount of carbon dioxide that was previously exhaled. These factors enhance the frequency and depth of breathing, and they may exacerbate the COVID-19 problem if infected persons using masks disseminate more contaminated air.[8-10]

The cause of secondary polycythemia may be congenital, acquired, or idiopathic. Causes of acquired secondary erythrocytosis include hypoxia, tumors (pheochromocytoma, cerebellar hemangioblastoma, paraganglioma, and uterine fibroids), kidney and liver diseases, Cushing's syndrome, and drugs.[11-13] Hemoglobin transports the most of oxygen (98%) through circulation. The oxygen-dissociation curve is crucial in human physiology that involves loading oxygen onto hemoglobin in the lungs and releasing oxygen from hemoglobin in tissues that need oxygen delivery. As a result, the body is able to sustain an oxygen saturation of 98%, with typical arterial hemoglobin saturation levels between 90% and 98%.[14,15] Erythropoietin (EPO) production is normally mediated by a decrease in hemoglobin (Hb)-oxygen saturation, a condition known as hypoxemia. Hypoxia causes some physiological reactions such as hyperventilation, increased heart rate, and stimulation of erythrocyte formation, all with the objective of sustaining normal arterial blood oxygen levels. Continuously using face masks for long hours in a day might cause intermittent hypoxia, which can affect Hb levels.[8,16,17]

A stricter hemoglobin cutoff was put into practice to detect masked PV with the WHO 2016 myeloproliferative neoplasm criteria.[18] These changes are supported by evidence, however, in the case of the COVID-19 pandemic, greater referral for high hemoglobin and JAK2 testing may be expected due to the use of face masks.

Here, we aimed to investigate the frequency of patients applying for high hemoglobin and tested for possible PV in the pandemic era.

Methods

The study was approved by the local Ethics Committee approval number 2021-07/1301. This study was also acknowledged and approved by the hematology department and medical genetics department.

Patients

We collected patients who applied to the general hematology outpatient clinic between March 2019 and April 2021 for the study. The research was carried out at a single center at Ankara Oncology Training and Research Hospital. We divided the patients into two groups according to before and after the pandemic. The transition period, March 2020–June 2020 was excluded. The inclusion criteria were based on ordering JAK2 mutation for polycythemia, being over 18 years of age and the exclusion criteria were requesting a JAK2 mutation with consideration of other myeloproliferative diseases, patients with known preexisting polycythemia, having a concomitant malignancy, and being under 18 years of age.

Data

We collected demographic data such as age and sex, laboratory parameters such as complete blood count and EPO level, concomitant diseases, smoking history, and spleen size. All patients' blood samples were collected in an Ethylenediaminetetraacetate anticoagulant tube, and PCR was done using allele-specific primers to check for a G-T point mutation (V617F) in the JAK2 gene on chromosome 9.

Statistical analyses

The analyses were carried out using IBM SPSS Statistics for Windows (Armonk, NY; version 26.0). To display patient and disease characteristics, descriptive statistics were used. Continuous variables were represented by a median (minimum–maximum) and categorical variables by a number and a percentage. Mann–Whitney U test was used to compare continuous variables, and Chi-square test was used to compare categorical variables. $P \leq 0.05$ was regarded as statistically significant.

Results

The median age of the cohort was 41 (16–83) years. Groups were different regarding age ($P = 0.04$). Groups were similar regarding gender ($P = 0.350$). Comorbidities were similar in both groups. Smoking was more frequent in the pre-COVID era group ($P = 0.046$). The characteristics of the groups were demonstrated in Table 1.

White blood count, red blood cell (RBC), hemoglobin, hematocrit levels, platelet, and EPO levels were similar among the groups. Splenomegaly did not differ between groups. JAK2 positivity was rare in both groups 5.9% versus 3.9% and was not statistically significant. JAK2 allele burden was higher in the COVID era group, but

it was not significant (P = 0.79). We also investigated the frequency of JAK2 test order in total outpatient examinations. It was 102 examinations out of 7920 for the pre-COVID era and 152 examinations out of 6087 for the COVID era; this was statistically significant ($P < 0.001$). The laboratory details were shown in Table 2.

Discussion

We have observed that the referral to the outpatient clinic for high hemoglobin was increased in the pandemic era. These patients were younger and less smokers. Other characteristics were similar to the prepandemic era.

To prevent the spread of SARS-CoV-2, the CDC issued a recommendation on April 3, 2020, advising the general public to use cloth face masks when outside, particularly those who live in regions with substantial SARS community transmission.[7] The most essential advantage of universal masking is protecting from asymptomatic, presymptomatic, and mildly symptomatic carriers. Regular mask use is usually not found very comfortable and makes breathing somewhat difficult.[19] A previous study reported the effect of masks on healthy health-care professionals as participants walked slowly on a treadmill for 1 h. They found no effect on respiration, with no effect on respiratory rate, tidal volume, or total ventilation.[20] The researchers noted a 3% rise in inhalation and exhalation resistance, which was most likely triggered by moisture preserved by the mask. This resistance implies that more air force is required, which may result in an increase in respiratory muscle usage. The analyses showed that these alterations were small and that the person wearing the mask would be unlikely to notice them.[21] These studies indicate that while wearing a mask increases breathing resistance somewhat; it has no effect on the tidal volume or breath frequency. However, these studies were carried out in a small amount of time, 1 h–4 h, and with N95 masks. It is not appropriate to generalize these conclusions to the population.

Hemoglobin transports the most of oxygen (98%) through circulation. In human physiology, the oxygen-dissociation curve is critical. Despite variations in the partial pressure of oxygen in the lungs, changes in arterial oxygen concentrations are hardly recorded because the oxygen-dissociation curve is frequently flattened at the peak. As a result, the body is able to sustain an oxygen saturation of 98%, with typical arterial hemoglobin saturation levels between 90% and 98%. Small variations in hemoglobin partial pressure cause oxygen to be released from hemoglobin and supplied to the active tissue due to the steep slope.[14,15] A study of surgeons using surgical masks found that arterial O2 saturation dropped from around 98% presurgery to 96% postsurgery, which lasted anywhere from 1 h to 4 h. A rise in heart rate from 85 beats/min presurgery to 90 beats/min postsurgery was also seen.[22] Another report investigated the effects of N95 masks alone versus N95 masks with a surgical mask overlay in nurses over the course of a 12-h shift. During the 12-h shift, both groups had increased transcutaneous CO2. However, while CO2 increases were statistically significant after the 12-h shift, the changes are unlikely to be clinically relevant, as CO2 levels remained within normal limits (45 mmHg). During the 12-h shifts, there were no changes in blood oxygen concentrations or blood pressure.[23] Wearing a medical

Table 1: Patient characteristics

	Pre-COVID Era (*n*=102)	COVID-Era (*n*=152)	*P*
Age (median) (minimum-maximum)	45 (16-83)	39 (16-83)	0.040*
Gender (male/female)	92/10	142/10	0.350
Comorbidity, *n* (%)			
Lung disease	7 (6.8)	6 (3.9)	0.283
CVD	8 (7.8)	4 (2.6)	0.055
DM	8 (7.8)	11 (7.2)	0.857
HT	17 (16.6)	25 (16.4)	0.906
Smoking	71 (69.6)	87 (57.2)	0.046*

*P<0.05 was regarded as significant. Calculated with Mann-Whitney *U* test. CVD=Cardiovascular disease, DM=Diabetes mellitus, HT=Hypertension

Table 2: Patient laboratory

	Median (minimum-maximum)		*P*
	Pre-COVID Era (*n*=102; 100%)	COVID-Era (*n*=152; 100%)	
WBC (×10^3 cells/μL)	8015 (1920-20,670)	7455 (4690-19,500)	0.073
RBC (×10^6 cells/μL)	5.75 (4.86-8.51)	5.8 (4.76-7.56)	0.215
HGB (g/dl)	17.4 (14.8-20.5)	17.3 (14.3-22.6)	0.376
HCT (%)	51.9 (44.9-69.6)	52 (42.4-72.7)	0.770
PLT (×10^3 cells/μL)	239 (150-768)	243.5 (132-889)	0.801
EPO (mIU/ml)**	7.45 (1-23.6)	9 (1–56)	0.223
Spleen enlargement (present), *n* (%)	5 (4.9)	9 (5.9)	0.72
JAK2 test orders/examinations	102/7920	152/6087	0.001*
JAK2 positive cases, *n* (%)	6 (5.9)	6 (3.9)	0.476
JAK2 v617F allele burden (%)***	8,5 (2-45)	16 (2-35)	0.79

*P<0.05 was regarded as significant, **EPO range 4.3-29.0 mIU/mL, ***For JAK 2-positive cases. Calculated with Mann-Whitney *U* and Chi-square tests. WBC=White blood count, RBC=Red blood cell, HGB=Hemoglobin, HCT=Hematocrit, PLT=Platelets, EPO=Erythropoietin, JAK 2=Janus kinase 2

mask does not appear to affect blood oxygen or carbon dioxide concentrations, according to investigations.[15,22,23] RBC is one of the guiding parameters in polycythemia cases. RBC increase supports PV. In our study, the normal RBC value excludes the diagnosis of PV.[24] We targeted to indirectly measure the effect of the pandemic. We spotted how many patients were referred for high hemoglobin and tested for PV with JAK2 mutation analysis. Compared to the literature, the laboratory parameters were the same prepandemic and pandemic era, however, our cohort is not a paired sample, so these findings are a matter of debate. We especially found out that more patients were referred for high hemoglobin and these patients were younger and less smokers. These findings are supporting our hypothesis.

Limitations of the study were that we did not have records such as prepandemic vital signs or laboratory results of patients. Our cohort is not paired; we had a heterogeneous patient population. The duration of using a face mask daily is very individual and not standard. The positive aspects of the study were we have a standardized approach for high hemoglobin evaluations and ordering JAK2 tests.

In conclusion, clinicians may need to re-evaluate the threshold of hemoglobin levels to order JAK2 tests in the pandemic era, and the significance of mildly elevated hemoglobin may be neglected while testing for potential PV.

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Conflicts of interest
There are no conflicts of interest.

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