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ORIGINAL ARTICLE

# Nail and hair findings developing in patients treated for COVID-19 infection fluorescence of keratinized tissues on Wood's lamp in COVID-19 disease

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## Abstract

**Background:** The new severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) is the causative agent of coronavirus 2019 (COVID-2019) disease. A wide variety of symptoms of the disease has been frequently reported in the literature in recent years. However, information on the findings in keratinized tissues is still limited. Data on changes in keratinized tissues such as nails, teeth and hair, and oral mucousa due to drugs used in the treatment of this disease are also extremely insufficient.

**Aim:** With this study, it was aimed to evaluate the changes in the keratinized tissues of our patients with COVID-19, who are frequently encountered in the Ear Nose and Throat outpatient clinic.

**Materials and Method:** The study was carried out on patients who applied to Başkent University Ear Nose and Throat clinic. There were 3 groups. The first group consisted of patients diagnosed with COVID-19 and received relevant medical treatments, the second group included individuals who have never experienced COVID-19 infection but have been vaccinated against COVID-19, and the third group is the control group with normal healthy individuals who have never been diagnosed with COVID-19 infection and have not been vaccinated so far. With the Wood's lamp, fluorescent changes in nails, hair, tooth, and the oral mucousa were recorded.

**Results:** A total of 124(75 females, 49 males) patients were included in the study. Positive Wood's finding was significantly higher in COVID-19 group(Group 1) who received Favipravir when compared with individuals who did not receive Favipravir ($p < 0.001$). Wood's positivity was not detected in any of the individuals who did not use favipravir. The rate of determining Wood's positivity in favipravir users decreases after 58 days.

**Discussion:** Accordingly, Favipravir accumulation in the kretainized tissues manifest positive Wood's sign in our study.

**Conclusion:** The adverse effects of the accumulation of the drugs—mainly Favipravir—used in the treatment of COVID-19 disease, have not yet been clearly demonstrated so far. Revealing the findings in these tissues with this study will pave the way for investigating changes or drug sequestrations in other organs in the long term.

KEYWORDS
Covid-19, favipravir, hair, nail, Wood's lamp

  

## 1 | INTRODUCTION

The pandemic of the coronavirus disease 2019 (COVID-19) was declared by World Health Organization (WHO) on March 11, 2020. Since then, numerous studies have been and are still being conducted on the symptoms, signs, diagnosis, and treatment of this disease. In addition to the main symptoms of fever, cough, and dyspnea, various different complaints such as anosmia, ageusia, and diarrhea are also observed. In this disease, there may be symptoms and signs related to the involvement of many organs. Dermatological complaints associated with COVID-19 are erythematous, vesiculous, and urticarial lesions. However, our information on nail findings is relatively rare. Moreover, findings in keratin tissues following the initiation of drug treatments for COVID-19 are also scarce in the literature, which includes several case reports and letters. Evaluation of keratinized tissues in drug tests seems to have advantages to urine and blood examinations. Drug concentrations in serum and urine decrease rapidly; however, drug accumulation in keratinized structures may last for months.[1]

In this study, it was aimed to evaluate the changes in hair, nails, teeth, and oral mucosa in patients diagnosed with COVID-19, using Wood's lamp, To our knowledge, our study is the first clinical research conducted in this sense.

## 2 | MATERIALS AND METHODS

The study was conducted in Başkent University Hospital Otolaryngology department between March and August 2021. All procedures performed in studies involving human participants were per under the ethical standards of the institutional and/or national research committee (Başkent University Institutional Review Board and Ethics Committee Project no: 21/126) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from the patients who participated in this clinical investigation.

A total of 124 patients were enrolled in the study, There were 3 groups, Group I included patients who were diagnosed with COVID-19 and received medical therapies. Group II consisted of patients who received Sinovac vaccine (Sinovac/China National Pharmaceutical Group) twice. This group of patients had never been diagnosed with COVID-19. The third group, included healthy individuals, who were neither diagnosed with COVID-19 nor vaccinated.

- Patients who have received drugs other than the ones for Covid-19 treatments within the last 6 months.
- Those who have been vaccinated with different vaccines developed for COVID-19.
- Patients who have nail polish, nail polish-like substances during their physical examination.
- Patients undergoing dental treatments.
- Patients with additional chronic oral mucousal pathologies, skin and/or nail, related dermatological diseases, or patients with red half-moon nail sign due to COVID-19.
- Drug abusers.
- Patients who have history of occupational exposure to some metals, elements etc. (i.e. arsenic intoxication) were excluded from the study.

Patients who applied to our clinic were evaluated by using Wood's lamp together with a senior dermatologist who was blinded to the study. Hair, nails, teeth, and oral mucosa of the patients were examined for fluorescent sign. This procedure was performed once for each patient.

The Wood's lamp examination was performed in accordance with the established instructions.[2] The yellow–white fluorescence sign was considered as "positive"[3] (Figures 1–3). The tablet was evaluated in its whole, fragmented, and dissolved (in water) forms under Wood's lamp. The dissolved form was compared to the dissolved form of another drug (Figures 4–6).

Favipravir (Fujifilm Toyama Chemical Co. Ltd.) therapy with a dose of 1600 mg twice daily on Day 1, followed by 600 mg twice daily for 5 days, is the recommended protocol for COVID-19 disease.[4] Patients who have received this drug as suggested were noted as "full dose users." Patients who have taken lower doses and patients who have used hidroxychloroquine were also noted.

The demographic characteristics of all patients, their complaints during COVID-19 infection, the date they started treatment with the diagnosis of COVID-19, the date they applied for the examination, the time elapsed between the two (days), the drugs that were taken during the treatment, and whether the drugs were taken in the appropriate dose and duration were recorded.

In the light of the results, findings of Wood's lamp and it's association with;

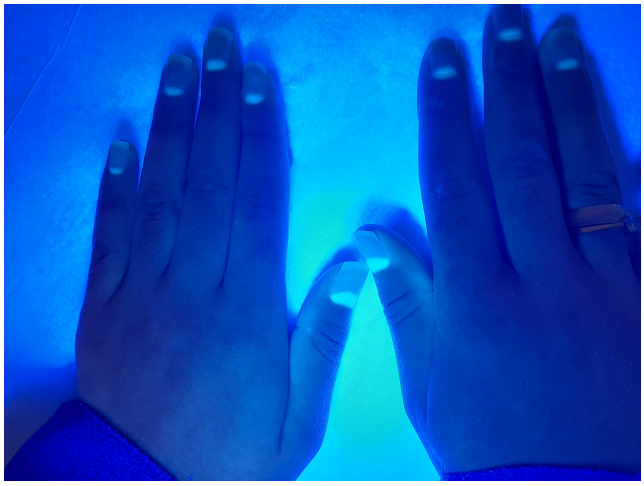

**FIGURE 1** Yellow–white fluorescence in fingernails under Wood's lamp is demonstrated

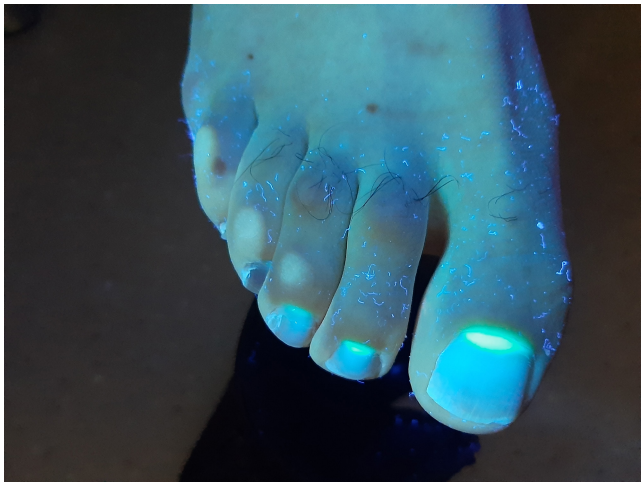

FIGURE 2 Yellow–white fluorescence in toenails under Wood's lamp is demonstrated

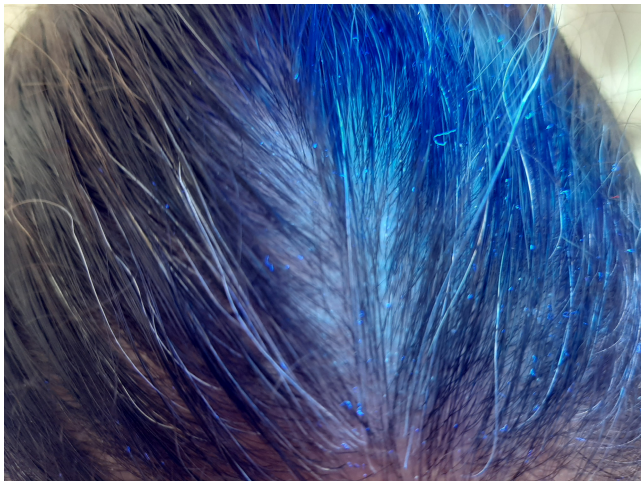

FIGURE 3 Yellow–white fluorescence in the hair under Wood's lamp is demonstrated

- Covid-19 infection.
- the drugs used for Covid-19 infection.
- the Sinovac vaccine were analyzed.

Statistical analyses were carried out with the help of the SPSS version 17.0 program. The suitability of variables to normal distribution was examined with histogram graphics and Kolmogorov–Smirnov tests. While presenting descriptive analyses, mean, standard deviation, and median (min/max) values were used. The variables that are not normally distributed (non-parametric) were evaluated between the two groups, the Mann–Whitney *U* test was used. Kruskal–Wallis Test was used when evaluating between more than two groups. Determining the cutoff levels for WOOD positivity, ROC analysis was used. Results with a *p*-value below 0.05 were considered as statistically significant.

FIGURE 4 Appearance of the complete form of favipravir under Wood's lamp is shown

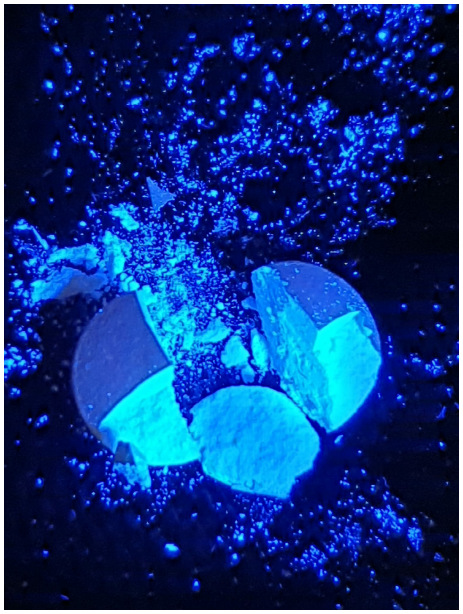

FIGURE 5 Fragmented form of favipravir shows yellow–white fluorescence under Wood's lamp

## 3 | RESULTS

A total of 124 patients (75 females, 49 males) were enrolled. There were 33, 33, and 38 individuals in Group I, II, and III, respectively. The mean years of age of the patients in each group is demonstrated in Table 1. Accordingly, the mean age of Group II is significantly

FIGURE 6 Dissolved form of favipravir (marked with an arrow) shows yellow–white fluorescence under Wood's lamp. The other drug showed no fluorescence

higher than the mean ages of Group I and Group III ($p < 0.001$) (Table 1). The mean time elapsed between the dates of diagnosis of COVID-19 and application to our clinic is 91.23 ± 73.63 days. While the mean time between diagnosis and admission to the clinic was 32.32 days in patients with positive fluorescent findings in Group 1, this period was 124.15 days in patients without fluorescent findings ($p < 0.001$).

The positive fluorescence sign was significantly higher in Group I compared with Group II and Group III ($p < 0.005$). In addition, no Wood's lamp findings were found in the vaccinated group (Group II) and control group (Group III) ($p < 0.005$) (Table 1). In patients with Wood positivity, findings were observed either in both the hair and nails or only in the nails. There were no findings in oral mucosa and tooth in any of the patients.

In the group with Covid-19 disease (Group I), no statistical significant relationship was observed between variable symptoms and the fluorescent sign. However, patients with anosmia–ageusia are significantly more likely to have fluorescent findings in both hair and nails compared to those without ($p = 0.019$) (Table 2).

In Group I, the time between diagnosis and visit to the ENT clinic was significantly lower in Wood's-positive patients compared with Wood's-negative patients ($p$ 0.001).

Considering the compliance with the medications, there were 3 patients in Group I, who did not receive any pharmacological agent during the course of illness. There was no remarkable Wood's lamp sign in their examinations. Positive Wood's finding were observed in 18 (41.86%) of 43 patients using favipravir at full dose. There are 6 patients who did not use favipravir at the full doses, and Wood's positivity was not observed in any of these patients. Only 1 patient in Group I was hospitalized for severe symptoms and signs and received hydroxychloroquine, corticosteroids, and favipravir. She had yellow–white fluorescent signs in her nails. Another patient received azithromycine and mucolytic therapy in addition to favipravir. Fluorescent staining was also observed on her nails.

Two patients received favipravir treatment twice due to the severity and prolongation of the symptoms. These patients applied to us on Day 45 and on Day 212 following the diagnosis. While positive fluorescent findings were observed in the nail in the patient who applied on Day 45, no findings were observed in the other patient.

In Group I, 50 patients have used favipravir, Of them, only 38% ($n = 19$) have fluorescent signs There was no significant relationship between the use of favipravir and Wood's positivity in Group I. However, among all groups, Wood's positivity rate was significantly higher in favipravir users compared with non-users ($p < 0.001$). In addition, 100% of the patients with Wood positivity used the drug favipravir ($p < 0.001$) (Table 3).

When we examined the tablet under the Wood's lamp, we observed fluorescence in its splitted and dissolved forms. We dissolved an anti-depressant tablet as well to compare the dissolved form of favipravir, and the fluorescence of favipravir was apparently observed while it was not detected in the other dissolved tablet (Figure 6).

Looking at the cutoff values for the visibility of fluorescent findings, it is found to decrease on Day 58 following the diagnosis (Table 4).

## 4 | DISCUSSION

Wood's lamp has been used for many years in the diagnosis of many dermatological diseases. It produces ultraviolet (UV) light. Fluorescence is the emission of electromagnetic radiation as a result of the excitation of molecules following the absorption of radiation of certain wavelengths.[5]

Margo and Deveze found that the skin with normal keratinization is seen fluorescent blue under Wood's lamp.[6] They also reported many different fluorescent appearances of various dermatological pathologies with Wood's lamp examination. Kayıran et al.[3] reported yellow–white fluorescence in nails and hair of four patients who were treated with favipravir for COVID-19 disease. They observed no such sign in their fifth patient who did not receive favipravir. Gülseren et al.[7] reported 3 patients with COVID-19, who had yellow–white fluorescence in their fingernails. Their 4th case who recovered without systemic therapy, had no fluorescence in his fingernails. Similarly, they had one patient who used favipravir and hydroxychloroquine together during the course of the disease, and he had fluorescence in his nails. The patients applied 1 month, 2 months, and 3 months after the diagnosis of COVID-19, respectively. Accordingly, while the fluorescent findings were in the proximal nail in the patient who was diagnosed 1 month ago, this finding was observed in the middle part of the nail in the patients who were seen in the 2nd and 3rd months after the diagnosis. In our study, the location of the fluorescence in the nails differs too. This is attributed to the growth of

**TABLE 1** The demographic data of the groups and the Wood's lamb positivity among groups were demonstrated

| | Group I | | Group II | | Group III | | Total | | *p* Value |
|---|---|---|---|---|---|---|---|---|---|
| | *n* | % | *N* | % | *n* | % | *n* | % | |
| Sex | | | | | | | | | |
| Male | 20 | (37.74) | 15 | (45.45) | 14 | (36.84) | 49 | (39.52) | 0.715 |
| Female | 33 | (62.26) | 18 | (54.55) | 24 | (63.16) | 75 | (60.48) | |
| Age | 44.30 ± 13.37 | 45.00 | 66.48 ± 14.69 | 68.00 | 41.26 ± 13.81 | 39.00 | 49.27 ± 17.29 | 50.00 | <0.001 |
| Vaccine | | | | | | | | | |
| Absent | 52 | (98.11) | 0 | (0.00) | 38 | (100) | 90 | (72.58) | <0.001 |
| Present | 1 | (1.89) | 33 | (100) | 0 | (0.00) | 34 | (27.42) | |
| COVID | | | | | | | | | |
| Absent | 0 | (0.00) | 33 | (100) | 38 | (100) | 71 | (57.26) | <0.001 |
| Present | 53 | (100) | 0 | (0.00) | 0 | (0.00) | 53 | (42.74) | |
| Wood's positivity | | | | | | | | | |
| Absent | 34 | (64.15) | 33 | (100) | 38 | (100) | 105 | (84.68) | <0.001 |
| Nail | 17 | (32.08) | 0 | (0.00) | 0 | (0.00) | 17 | (13.71) | |
| Hair & Nail | 2 | (3.77) | 0 | (0.00) | 0 | (0.00) | 2 | (1.61) | |
| Wood's positivity | | | | | | | | | |
| Absent | 34 | (64.15) | 33 | (100.00) | 38 | (100.00) | 105 | (84.68) | <0.001 |
| Present | 19 | (35.85) | 0 | (0.00) | 0 | (0.00) | 19 | (15.32) | |

*Note:* Chi-square test.

**TABLE 2** Wood's lamp positivity and it's relation with the symptoms and the use of favipravir in Group I was shown

| COVID-19 group (Group I) | Wood's positivity | | | *p* Value |
|---|---|---|---|---|
| | Absent | Nail | Hair & nail | |
| | *n* (%) | *n* (%) | *n* (%) | |
| Sex | | | | |
| Male | 14 (70.00) | 6 (30.00) | 0 (0.00) | 0.490 |
| Female | 20 (60.61) | 11 (33.33) | 2 (6.06) | |
| Vaccine | | | | |
| Absent | 33 (63.46) | 17 (32.69) | 2 (3.85) | 0.752 |
| Present | 1 (100.00) | 0 (0.00) | 0 (0.00) | |
| COVID-19 | | | | |
| Absent | 0 (0.00) | 0 (0.00) | 0 (0.00) | **>0.05** |
| Present | 34 (64.15) | 17 (32.08) | 2 (3.77) | |
| Symptom | | | | |
| Absent | 15 (78.95) | 4 (21.05) | 0 (0.00) | 0.197 |
| Present | 19 (55.88) | 13 (38.24) | 2 (5.88) | |
| Cough | | | | |
| Absent | 30 (63.83) | 15 (31.91) | 2 (4.26) | 0.876 |
| Present | 4 (66.67) | 2 (33.33) | 0 (0.00) | |
| Miyalgia/Atralgia | | | | |
| Absent | 26 (66.67) | 11 (28.21) | 2 (5.13) | 0.460 |
| Present | 8 (57.14) | 6 (42.86) | 0 (0.00) | |
| Anosmia-Ageusia | | | | |
| Absent | 28 (66.67) | 14 (33.33) | 0 (0.00) | **0.019** |
| Present | 6 (54.55) | 3 (27.27) | 2 (18.18) | |
| Fever | | | | |
| Absent | 30 (68.18) | 12 (27.27) | 2 (4.55) | 0.231 |
| Present | 4 (44.44) | 5 (55.56) | 0 (0.00) | |
| Weakness/Tiredness | | | | |
| Absent | 26 (65.00) | 12 (30.00) | 2 (5.00) | 0.642 |
| Present | 8 (61.54) | 5 (38.46) | 0 (0.00) | |
| Vertigo/dizziness | | | | |
| Absent | 34 (66.67) | 15 (29.41) | 2 (3.92) | 0.111 |
| Present | 0 (0.00) | 2 (100.00) | 0 (0.00) | |
| URSI symptoms | | | | |
| Absent | 33 (66.00) | 15 (30.00) | 2 (4.00) | 0.411 |
| Present | 1 (33.33) | 2 (66.67) | 0 (0.00) | |
| Headache | | | | |
| Absent | 31 (64.58) | 16 (33.33) | 1 (2.08) | 0.128 |
| Present | 3 (60.00) | 1 (20.00) | 1 (20.00) | |
| Breathing disorder | | | | |
| Absent | 28 (62.22) | 15 (33.33) | 2 (4.44) | 0.713 |
| Present | 6 (75.00) | 2 (25.00) | 0 (0.00) | |
| Favipravir use | | | | |
| Favipravir not used | 3 (100.00) | 0 (0.00) | 0 (0.00) | 0.251 |
| Favipravir full dose user | 25 (58.14) | 16 (37.21) | 2 (4.65) | |
| Favipravir + hydroxychloroquine | 0 (0.00) | 1 (100.00) | 0 (0.00) | |
| Favipravir incomplete use | 6 (100.00) | 0 (0.00) | 0 (0.00) | |

*Note:* Chi-square test.

Abbreviation: URSI, upper respiratory system infections.

Bold indicates statistically significant *p* values.

**TABLE 3** Association between Wood's sign positivity and the use of favipravir is demonstrated

| | Favipravir use | | *p* Value |
|---|---|---|---|
| | Favipravir not used | Favipravir used | |
| | *n* (%) | *n* (%) | |
| Wood's positivity | | | |
| Absent | 74 (100.00) | 31 (62.00) | **<0.001** |
| Present | 0 (0.00) | 19 (38.00) | |

*Note:* Chi-Square test.

Bold indicates statistically significant *p* values.

the nails. In this current study, the fluorescence was not observed in the hair of all patients with a positive Wood's sign on their nails. Also the fluorescence findings differed even in finger and toenails. The rates of growth in fingernails, toenails, and hair are 0.1 mm/day, 0.03–0.04 mm/day, and 1 cm/day, respectively.[8–10] We think that this is due to the differences in hair and nail growth rates. However, further studies are required.

Besides many cutaneous manifestations of COVID-19 disease, there are case reports of nail findings.[11–13] As Akl et al.[13] mentioned in their review, various nail findings (i.e., leukonycia, onychomadesis, and red half-moon sign) may be observed in COVID-19 pandemic. Neri et al.[11] defined the "red half-moon nail sign." in which convex red-colored changes in the nail at the distal edge of the lunula are observed. The patients do not have any additional nail complaints. This is thought to be due to microvascular damage secondary to vascular inflammation.[11,14] In our patients, there was neither any dermatological pathology nor red half-moon nail sign at the time they applied to the clinic.

Hydroxychloroquine is a pharmacological agent that has been on the market for many years, used in many rheumatological diseases besides malaria. For this reason, its antiviral effectiveness has been questioned during the pandemic process, and its use in both prophylaxis and treatment has come to the fore for a while. It has dermatological side effects such as erythroderma, itching, hair loss, and increased sensitivity to the sun, but to our knowledge, there was no data regarding fluorescent changes in hair and nails. Also, remdesivir, dexamethasone, convalescent plasma, and tocilizumab have not been associated with nail and hair fluorescence-like changes in the literature so far.[15] One of our patients used hydroxychloroquine and dexamethasone in addition to favipravir. Her positive Wood's lamp signs seem more likely to be related to favipravir.

Favipravir is a RNA dependent RNA polymerase inhibitor, which has been reported effective in inhibition of various RNA viruses.[16] Prospective randomized trials for favipravir have been conducted since the early stages of COVID-19 pandemic. In March 2020, it was reported to be effective against COVID-19. Although there are still debates about the effectiveness of its use, it became one of the most frequently used drugs worldwide for the treatment of COVID-19 disease.[17,18] Hyperuricemia, QTc prolongation and teratogenity are associated with the use of this agent, and short-term use is advocated. Doran et al.[19] reported ocular surface fluorescence in their patient following favipravir treatment for COVID-19. The patient had visual impairment which started with the initiation of favipravir therapy and resolved after cessation of it. Ocular surface fluorescence diminished two weeks after the favipravir therapy; however, nail fluorescence in their patient persisted. They examined the drug in its whole, splitted, and dissolved forms under UV, and observed fluorescence in the second and third forms. They did not evaluate their patient under Wood's lamp, but with a similar UV light source. The UV light source used in this report had 365–395 nm wavelength, while Wood's lamp has a wavelength between 320 and 400 nm.[20] Therefore, we also examined the favipravir tablet under Wood's lamp and, similar to that of Doran et al.,[19] we detected fluorescence in the fragmented and dissolved forms, while fluorescence was not observed in the whole tablet.

When we started this study, only the Sinovac vaccine was administered in our country. In order not to create bias in the study, patients vaccinated with Biontech (BNT162b2, Pfizer, Inc., and BioNTech)—an mRNA based COVID-19 vaccine—who entered the country later, were not included in the study. But we hope that further studies will be carried out with the Biontech vaccine, which is currently the most widely applied.

There are several limitations of our study. As the patients enter quarantine as soon as they are diagnosed with COVID-19, the first application to our clinic is 15 days after the diagnosis. Therefore, it was not possible to evaluate with Wood's lamp from the time they started using favipravir. Thus we do not yet know how long after treatment fluorescence is seen. Evaluation with Wood's lamp was made once in our patients. Studies in which patients are examined more frequently are needed.

**TABLE 4** On the day 58, after the diagnosis of COVID-19, the possibility of visualizing fluorescent sign with Wood's lamb decreases

| | Area | Std. error[a] | *p* Value | Asymptomatic 95% confidence interval | | Cut-off | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Lower bound | Upper bound | | | | | |
| Time | 0.923 | 0.036 | 0.000 | 0.851 | 0.994 | <58 | 100% | 82.35% | 76% | 100% |

*Note:* ROC analyses.

[a]Under the nonparametric assumption.

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; Std, standard.

## 5 | CONCLUSION

The findings show that favipravir accumulates in various tissues. It is not clear which substances in it cause this fluorescent finding. Further pharmacologic studies are required. In our study, none of the patients had complaints of hair, nails, teeth, or oral mucosa. However, the possible long-term side effects of this drug should be followed up with prospective studies with large patient series.

### CONFLICT OF INTEREST

The authors of this study declare no conflict of interest.

### ETHICAL APPROVAL

This study was approved by Baskent University Institutional Review Board and Ethics Committee (Project no: 21/126) and supported by Baskent University Research Fund.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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