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Autologous hematopoietic stem cell transplantation (ASCT) is indicated as a consolidative treatment after induction and/or salvage therapy of various hematologic malignancies, including multiple myeloma and other plasma cell disorders, Hodgkin lymphoma, and non-Hodgkin lymphomas [1].

Coronavirus disease 2019 (COVID-19), caused by a single-stranded RNA β coronavirus, named as 2019 novel coronavirus (2019-nCoV), forced the World Health Organization to declare it a pandemic on March 11, 2020. It has led to serious chaos all over the world and has been a significant cause of morbidity and mortality [2]. ASCT processes were also adversely affected during this difficult and exhausting period. Some candidate patients lost their chance of ASCT due to COVID-19-related mortality (CRM) and morbidities. The disruptions in treatment schedules due to the emergence of COVID-19 during pre- and post-transplant periods caused additional morbidity and mortality. The cancellation of hospital visits to decrease the risk of transmission, temporary reductions in the number of health personnel, and so forth also ended up with disruptions in medical care and follow-up [3].

ABSTRACT
This study aimed to retrospectively determine the frequency and prognosis of coronavirus disease 2019 (COVID-19) in patients who underwent an autologous stem cell transplantation (ASCT) during the pandemic and to evaluate the effects of possible factors on outcomes.

The demographic characteristics, diagnoses, COVID-19 status, vaccination status, COVID-19-related mortality (CRM), non-relapse mortality (NRM), and overall survival (OS) of patients who underwent an ASCT in our center between March 2020 and June 2022 were investigated.

Of the 153 patients who underwent ASCT consecutively, 146 patients were included in this study and the rest were excluded. The median age of the 146 patients was 55 years (20–78 years), and the median follow-up time after ASCT was 17.4 months. The common diagnoses were multiple myeloma and other plasma cell disorders (44.5%, n = 65) and Hodgkin lymphoma (15.1%, n = 22). Of the patients, 8.9% (n = 13) had COVID-19 before ASCT and 24.0% (n = 35) after ASCT, and 6.2% (n = 9) had CRM. Unvaccinated patients constituted 25.3% (n = 37). Moreover, 19.2% patients were vaccinated at least once before ASCT n = 28), 44.5% (n = 65) got vaccinated after ASCT, and 11.0% (n = 16) got vaccinated both before and after ASCT. The cumulative CRM after 3, 6, 9, and 12 months was 2.0% [95% confidence interval (CI): 0.04 vs 3.96], 5.0% (95% CI: 1.08–8.92), 6.0% (95% CI: 2.08–9.92), and 6.0% (95% CI: 3.08–10.92), respectively. Patients with ≥3 doses of vaccination had favorable CRM (P = 0.01), NRM (P = 0.001), and OS (P < 0.001). Age ≥60 years, non-Hodgkin lymphoma, and a total vaccination dose of ≤2 were independently associated with a poorer OS and higher NRM. A total vaccination dose of ≤2 was an independent factor for increased CRM (hazard ratio: 9.69; 95% CI: 1.20–78.15; P = 0.03).

COVID-19 is an important cause of mortality in the post-ASCT period. The mortality risk was higher during the 6 months after ASCT. Those who received at least two doses of the vaccine exhibited improved outcomes. Booster doses after ASCT might have a positive impact.

Key words: Autologous transplantation, COVID-19, mortality

INTRODUCTION
Autologous hematopoietic stem cell transplantation (ASCT) is indicated as a consolidative treatment after induction and/or salvage therapy of various hematologic malignancies, including multiple myeloma and other plasma cell disorders, Hodgkin lymphoma, and non-Hodgkin lymphomas [1].

Coronavirus disease 2019 (COVID-19), caused by a single-stranded RNA β coronavirus, named as 2019 novel coronavirus (2019-nCoV), forced the World Health Organization to declare it a pandemic on March 11, 2020. It has led to serious chaos all over the world and has been a significant cause of morbidity and mortality [2]. ASCT processes were also adversely affected during this difficult and exhausting period. Some candidate patients lost their chance of ASCT due to COVID-19-related mortality (CRM) and morbidities. The disruptions in treatment schedules due to the emergence of COVID-19 during pre- and post-transplant periods caused additional morbidity and mortality. The cancellation of hospital visits to decrease the risk of transmission, temporary reductions in the number of health personnel, and so forth also ended up with disruptions in medical care and follow-up [3].
Despite the efforts aiming to prevent the spread of the infection with social and individual measures, such as filiation, isolation practices, mask use, social distancing, and personal hygiene, the most successful intervention in the course of the pandemic was the discovery of effective vaccines against COVID-19 [4]. However, the low efficacy of these vaccines in patients with immunosuppression is still a cause of great concern [5]. Sinovac (CoronaVac), an inactivated whole virus (iWV) vaccine, was the first available vaccine in Turkey [6]. The Pfizer BionTech vaccine, which is a messenger ribonucleic acid (mRNA) vaccine produced with new technology, started to be used shortly after [7]. Recently, another iWV vaccine, Turkovac, has become a third option [8]. The positive effects of vaccination provided a big success despite concerns about vaccine-related side effects, vaccine hesitancy, and so forth [9]. Following the decline in the rates of new cases and deaths, a normalization process started all over the world. As of April 14, 2021, the Turkish administration declared a gradual lifting scheme for anti-COVID-19 measures [10]. The mandates were completely lifted on April 9, 2022 [11]. However, the current situation does not mean that COVID-19 has disappeared. The negative effects of the pandemic still continue and COVID-19 still remains a concern, especially in patients with immunosuppression.

This study aimed to retrospectively determine the frequency and prognosis of COVID-19 in patients who underwent an ASCT in our center during the pandemic and evaluate the possible factors that might affect the outcomes, including patient and disease characteristics and vaccination status for COVID-19.

MATERILAS AND METHODS

Patients who underwent an ASCT in our center between March 2020 and June 2022 were evaluated retrospectively. The demographic characteristics of patients, diagnosis, COVID-19 status and the course of infection, vaccination status for COVID-19, complications, and follow-up data were recorded. The study was approved by the local ethics committee of our hospital and conducted in accordance with the ethical standards specified in the Declaration of Helsinki.

The primary objective of the study was to determine the incidence of COVID-19 and CRM during the relevant period. The secondary objectives included the determination of non-relapse mortality (NRM) and overall survival (OS), and the evaluation of possible factors affecting them.

Three time periods were identified according to the date of ASCT: the pandemic period (between March 11, 2020, and April 13, 2021), the normalization process (between April 14, 2021, and April 8, 2022), and the period after complete lifting of mandates (after April 9, 2022). The median, minimum, and maximum values were given for non-normally distributed continuous variables. The frequencies and percentages were calculated for categorical variables. The comparisons between groups were made using the chi-square or Fisher test for categorical variables and the Mann–Whitney U test and Kruskal–Wallis test for continuous variables. The estimated median follow-up time was calculated by the reverse Kaplan–Meier method. OS was defined as the time from ASCT until death from any cause or last date of follow-up. CRM was defined as death after ASCT due to COVID-19 and its complications. NRM was defined as death after ASCT due to any cause, excluding the relapse of hematologic disease. The Kaplan–Meier method and log-rank test were used for survival estimates and intergroup comparisons, respectively. Multivariate analysis (MVA) was performed using the Cox proportional hazards assumption model to determine the effects of possible confounding factors on survival outcomes. For this purpose, factors with statistical significance (P < 0.05) in univariate analysis were entered into a Cox proportional hazards assumption model using the stepwise exclusion method and evaluated by residual analysis (Schoenfeld and Martingale) [12].

All statistical analyses were performed with the statistical software package IBM SPSS Statistics for Windows version 25.0 (IBM Corp. released 2017, NY, USA), and a 5% type 1 error (two-sided) was considered statistically significant.

RESULTS

Between March 2020 and June 2022, 153 consecutive ASCTs were performed in our center. After excluding 7 patients with missing follow-up data, the analyses were conducted for the remaining 146 patients.

The median age of the patients was 55 years (20–78 years). Male patients constituted 58.9% (n =
The estimated median follow-up time was 17.4 months [95% confidence interval (CI): 14.9–20.0]. The most common diagnoses were multiple myeloma and other plasma cell disorders (44.5%, n = 65) and Hodgkin lymphoma (15.1%, n = 22) (Table 1). Patients without any COVID-19 episode constituted 67.1% (n = 98), whereas 8.9% (n = 13) and 24.0% (n = 35) had at least one episode before and after ASCT, respectively. CRM was present in 6.2% (n = 9). Those who did not receive any vaccination constituted 25.3% (n = 37), whereas 15.8% (n = 23) received only iWV vaccine, 30.1% (n = 44) only mRNA vaccine, and 28.8% (n = 42) both iWV and mRNA vaccines. Of the patients, 19.2% (n = 28) received at least one dose of vaccine before ASCT, 44.5% (n = 65) after ASCT, and 11.0% (n = 16) both before and after ASCT. The median time from ASCT to the first COVID-19 episode was 6 months (0–27). The median time from the last COVID-19 episode to ASCT was 5 months (1–19). Of the patients, 54.2% (n = 26) were vaccinated before the first COVID-19 episode (Table 1).

### Table 1 Characteristics of patients

| Age, median (minimum–maximum) | 55 (20–78) |
|---|---|
| Sex, n (%) | Male 86 (58.9)  
Female 60 (41.1) |
| Diagnosis, n (%) | Multiple myeloma and other plasma cell disorders 65 (44.5)  
Diffuse large B-cell lymphoma 15 (10.3)  
Mantle cell lymphoma 12 (8.2)  
Primary central nervous system lymphoma 15 (10.3)  
T-cell lymphomas 10 (6.8)  
Hodgkin lymphoma 22 (15.1)  
Others 7 (4.8) |
| Estimated median follow-up, months, (95% confidence interval) | 17.4 (14.9–20.0) |
| Transplantation period, n (%) | During the pandemic (between 11.03.2022 and 13.04.2021) 81 (55.5)  
During the normalization process (between 14.04.2021 and 08.04.2022) 57 (39.0)  
After lifting of mandates (after 09.04.2022) 8 (5.5) |
| COVID-19 episode, n (%) | None 98 (67.1)  
Before transplantation 13 (8.9)  
After transplantation 35 (24.0) |
| COVID-19-related mortality | 9 (6.2) |
| Total dose of iWV vaccine, n (%) | <2 86 (58.9)  
≥2 60 (41.1) |
| Total dose of mRNA vaccine, n (%) | <2 88 (60.3)  
≥2 58 (39.7) |
| Vaccination status, n (%) | None 37 (25.3)  
iWV vaccine only 23 (15.8)  
mRNA vaccine only 44 (30.1)  
Both iWV and mRNA vaccine 42 (28.8) |
| Vaccinated before the first COVID-19 episode, n (%) | 26 (54.2) |
| Vaccinated before/after transplantation, n (%) | None 37 (25.3)  
Before transplantation 28 (19.2)  
After transplantation 65 (44.5)  
Both before and after transplantation 16 (11.0) |
| Months from transplantation to the first COVID-19 episode, median (minimum–maximum) | 6 (0–27) |
| Months from the last COVID-19 episode to transplantation, median (minimum–maximum) | 5 (1–19) |

iWV: Inactivated whole virus; mRNA: messenger ribonucleic acid.
The distribution of age, diagnoses, and frequency of COVID-19 episodes was similar between groups when considered according to the vaccination status before and after ASCT (Table 2). Female patients were more likely to be unvaccinated (67.6%, n = 25) and to get vaccinated after ASCT (75.4%, n = 49) (P < 0.001; Table 2). More patients transplanted during the normalization process received vaccination both before and after ASCT (93.8%, n = 15), and received both types of vaccines (68.8%, n = 11) (P < 0.001 and P < 0.001, respectively) (Table 2). The distribution of age, sex, diagnoses, frequency of COVID-19 episodes, vaccination status, and total vaccination doses was similar among patients transplanted during the pandemic and after the normalization process (Table 3).

The cumulative CRM at 3, 6, 9, and 12 months after ASCT were 2.0% (95% CI: 0.04 vs 3.96), 5.0% (95% CI: 1.08–8.92), 6.0% (95% CI: 2.08–9.92), and 6.0% (95% CI: 3.08–10.92), respectively (Fig. 1). Patients with no vaccination and those vaccinated only before ASCT had higher CRM (P = 0.001) and NRM (P < 0.001), and lower OS (P < 0.001) (Figs. 2, 3, and 4, respectively). Patients with ≥3 doses of vaccination had favorable CRM (P = 0.01), NRM (P = 0.001), and OS (P < 0.001) (Figs. 5, 6, and 7, respectively). CRM was similar between patients with different diagnosis (P = 0.97, Fig. 8). However, patients transplanted for non-Hodgkin lymphoma had worse NRM (P < 0.05) and OS (P < 0.001) (Figs. 9 and 10, respectively). CRM was similar between younger and older patients (P = 0.19; Fig. 11). However, patients ≥60 years of age had worse NRM (P = 0.001) and OS (P = 0.001) (Figs. 12 and 13, respectively). CRM did not change during the pandemic and after the normalization process (P = 0.84; Fig. 14).

In MVA, being ≥60 years [hazard ratio (HR): 0.22, 95% CI: 0.11–0.43], ASCT for non-Hodgkin lymphoma (HR: 0.21, 95% CI: 0.10–0.44), and a total vaccination dose of ≤2 (HR: 0.11, 95% CI: 0.04–0.28) were independently associated with a poorer OS (P < 0.001, P < 0.001, and P < 0.001, respectively) (Table 4). Being ≥60 years (HR: 6.58, 95% CI: 2.30–18.80), ASCT for non-Hodgkin lymphoma (HR: 2.73, 95% CI: 1.03–7.25), and a total vaccination dose of ≤2 (HR: 6.23, 95% CI: 1.77–21.91) were also independently associated with a

Table 2 Distribution and characteristics of patients according to the vaccination status before and after transplantation

| Sex, n (%) | None | Vaccinated before transplantation | Vaccinated after transplantation | Vaccinated before and after transplantation | P |
|-----------|------|----------------------------------|---------------------------------|-------------------------------------------|---|
| Male      | 12 (32.4) | 15 (53.6) | 49 (75.4) | 10 (62.5) | <0.001 |
| Female    | 25 (67.6) | 13 (46.4) | 16 (24.6) | 6 (37.5)  |          |
| Age, median (minimum–maximum) | 50 (20–78) | 57 (30–77) | 55 (21–74) | 61 (34–75) | 0.09 |
| Diagnosis, n (%) | Non-Hodgkin lymphoma | 18 (48.6) | 20 (71.4) | 43 (66.2) | 10 (62.5) | 0.23 |
| Other     | 19 (51.4) | 8 (28.6)  | 22 (33.8) | 6 (37.5)  |          |
| Estimated median follow-up, months, (95% confidence interval) | 18.5 (13.2–23.7) | 5.2 (3.6–6.9) | 22.0 (21.1–22.9) | 9.4 (8.0–10.9) | <0.001 |
| Transplantation period, n (%) | During pandemic | | | | |
| During normalization and after | 27 (73.0) | – | 53 (81.5) | 1 (6.3)  | <0.001 |
| COVID-19 episode, n (%) | None | 26 (70.3) | 15 (65.2) | 26 (59.1) | 31 (73.8) | 0.61 |
| Before transplantation | 2 (5.4) | 1 (4.4)  | 6 (13.6)  | 4 (9.5)   |          |
| After transplantation | 9 (24.3) | 7 (30.4) | 12 (27.3) | 7 (16.7)  |          |
| Vaccine type, n (%) | None | 37 (100.0) | – | – | – | <0.001 |
| Only iWV vaccine | – | 8 (28.6) | 12 (18.5) | 3 (18.8)  |          |
| Only mRNA vaccine | – | 10 (35.7) | 32 (49.2) | 2 (12.5)  |          |
| iWV + mRNA vaccine | – | 10 (35.7) | 21 (32.3) | 11 (68.8) |          |
| Total vaccine dose, n (%) | 0–1 | 37 (100.0) | 1 (3.6)  | 8 (12.3)  | – | <0.001 |
| 2–3 | – | 23 (82.1) | 44 (67.7) | 7 (43.8)  |          |
| >3 | – | 4 (14.3)  | 13 (20.0) | 9 (56.2)  |          |

iWV, inactivated whole virus; mRNA, messenger ribonucleic acid.
Table 3 Distribution and characteristics of patients according to the transplantation period

|                          | During pandemic | After normalization process | P     |
|--------------------------|-----------------|-----------------------------|-------|
| Sex, n (%)               |                 |                             |       |
| Male                     | 47 (58.0)       | 39 (60.0)                   | 0.81  |
| Female                   | 34 (42.0)       | 26 (40.0)                   |       |
| Age, median (minimum–maximum) | 58 (20–78) | 53 (21–77) | 0.95  |
| Diagnosis, n (%)         |                 |                             |       |
| Non-Hodgkin lymphoma     | 52 (64.2)       | 39 (60.0)                   | 0.60  |
| Other                    | 29 (35.8)       | 26 (40.0)                   |       |
| Estimated median follow-up, months, (95% confidence interval) | 22.1 (21.3–23.0) | 9.0 (7.7–10.4) | <0.001 |
| COVID-19 episode, n (%)  |                 |                             |       |
| None                     | 56 (69.1)       | 42 (64.6)                   | 0.43  |
| Before transplantation   | 5 (6.2)         | 8 (12.3)                    |       |
| After transplantation    | 20 (24.7)       | 15 (23.1)                   |       |
| Vaccine type, n (%)      |                 |                             | 0.10  |
| Only iWV vaccine         | 11 (13.6)       | 12 (18.5)                   |       |
| Only mRNA vaccine        | 21 (25.9)       | 23 (35.4)                   |       |
| iWV + mRNA vaccine       | 22 (27.2)       | 20 (30.8)                   |       |
| Total vaccine dose, n (%)|                 |                             | 0.45  |
| 0–1                      | 29 (35.8)       | 17 (26.2)                   |       |
| 2–3                      | 39 (48.1)       | 35 (53.8)                   |       |
| >3                       | 13 (16.0)       | 13 (20.0)                   |       |

iWV, Inactivated whole virus; mRNA, messenger ribonucleic acid.

Table 4 Multivariate analysis of prognostic factors for overall survival, non-relapse mortality, and COVID-19-related mortality

| Parameters for overall survival | HR    | 95% CI     | P       |
|---------------------------------|-------|------------|---------|
| Age ≥60 years                   | 0.22  | 0.11–0.43  | <0.001  |
| Non-Hodgkin lymphoma            | 0.21  | 0.10–0.44  | <0.001  |
| Total vaccination dose ≤2       | 0.11  | 0.04–0.28  | <0.001  |

| Parameters for non-relapse mortality | HR    | 95% CI     | P   |
|--------------------------------------|-------|------------|-----|
| Age ≥60 year                         | 6.58  | 2.30–18.80 | <0.001 |
| Non-Hodgkin lymphoma                 | 2.73  | 1.03–7.25  | 0.04 |
| Total vaccination dose ≤2            | 6.23  | 1.77–21.91 | 0.004 |

| Parameters for COVID-19-related mortality | HR    | 95% CI     | P   |
|--------------------------------------------|-------|------------|-----|
| Age ≥60 years                              | 2.81  | 0.74–10.68 | 0.13 |
| Non-Hodgkin lymphoma                       | 1.03  | 0.25–4.31  | 0.97 |
| Total vaccination dose ≤2                  | 9.69  | 1.20–78.15 | 0.03 |

CI: Confidence interval; HR: hazard ratio.

higher NRM (P < 0.001, P = 0.04, and P = 0.004, respectively) (Table 4). A total vaccination dose of ≤2 was an independent factor for increased CRM (HR: 9.69, 95% CI: 1.20–78.15, P = 0.03) (Table 4).

DISCUSSION

Patients undergoing stem cell transplants are susceptible to viral infections and community-acquired respiratory viruses [13]. The concerns following the sudden emergence of the COVID-19 pandemic have led many transplant centers to postpone elective ASCTs, except for urgent conditions in concordance with the initial recommendations of international transplant societies including the European Society for Blood and Marrow Transplantation (EBMT) and American Society for Transplantation and Cellular Therapy [14, 15].

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Figure 1 Kaplan–Meier curve for COVID-19-related mortality.

Figure 2 COVID-19-related mortality according to the vaccination status ($P = 0.001$).

Figure 3 Non-relapse mortality according to the vaccination status ($P < 0.001$).
Figure 4 Overall survival according to the vaccination status ($P < 0.001$).

Figure 5 COVID-19-related mortality according to the number of vaccine doses administered ($P = 0.01$).

Figure 6 Non-relapse mortality according to the number of vaccine doses administered ($P = 0.001$).
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**Figure 7** Overall survival according to the number of vaccine doses administered ($P < 0.001$).

**Figure 8** COVID-19-related mortality according to diagnosis ($P = 0.97$).

**Figure 9** Non-relapse mortality according to diagnosis ($P < 0.05$).
Figure 10 Overall survival according to diagnosis ($P < 0.001$).

Figure 11 COVID-19-related mortality according to age groups ($P = 0.19$).

Figure 12 Non-relapse mortality according to age groups ($P = 0.001$).
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Figure 13 Non-relapse mortality according to age groups \( (P = 0.001) \).

Figure 14 COVID-19-related mortality according to the transplantation period \( (P = 0.84) \).

Figure 15 Non-relapse mortality according to the transplantation period \( (P = 0.77) \).
Current observations and reports have justified these concerns. The reported 28-day survival was 67% in patients who had COVID-19 after ASCT. The risk factors for mortality were as follows: age <50 years, male sex, and development of COVID-19 within 12 months after transplantation [16]. In another study, the 6-week OS after COVID-19 following ASCT was 72.1%. The reported risk factors for mortality were advanced age, poor performance status, and intensive care unit admission [17]. In a study of patients receiving cellular therapies including ASCT, the 30-day OS was 78% [18].

In a group of patients with hematologic cancers, lower mortality rates were reported among recipients of ASCT compared with nontransplanted patients (17% vs 31%) [19]. Because these studies did not involve a direct comparison with the general population, whether a relatively increased mortality risk existed was not clear. However, the reported absolute rates were even high enough. In addition, most of these studies included patients diagnosed in the early stages of the pandemic. Thus, how other treatments, such as remdesivir, corticosteroids, and systemic thromboembolism prophylaxis, and vaccination affected the prognosis was not clear [20].

The findings of this study added to the current literature because the study involved the outcomes of patients in the long-term follow-up. CRM was higher during the initial 3–6 months following ASCT and tended to reach a plateau 6–9 months after ASCT. This was an expected finding, considering the ongoing immunosuppression due to transplantation, the frequent use of post-ASCT therapies in this period, and the risks posed by the probably insufficient and/or reduced protection with previous doses of the COVID-19 vaccine. Although the results of this study could not be directly compared with those of the previous studies, the rate of CRM in this study was equally high.

Our center had a tendency to postpone elective transplantations, especially at the beginning of the pandemic, in accordance with the recommendations of national and international authorities, which resulted in a decrease in the total number of transplants and an altered selection of indications. Thus, a possible selection bias occurred, which might have had an additional negative effect on the NRM and OS rates. Inferior NRM and OS observed among patients ≤60 years of age and those with non-Hodgkin lymphoma might represent this bias. In concordance, MVA, in which inadequate vaccination was found to be the only independent risk factor for CRM, failed to show an effect of age and diagnosis on CRM. The observed high NRM rates might also be due to yet unexplained COVID-19-related complications.

Vaccination has been a milestone in the COVID-19 pandemic. However, our knowledge regarding COVID-19 vaccination in immunocompromised patients is still insufficient, as these patients are generally excluded from clinical trials. The response to the first dose of vaccine in patients with solid tumors and hematologic cancers was very low compared with that in healthy controls (13%–39% vs 97%), but higher responses were obtained after a booster dose [21].
our practice, we recommend COVID-19 vaccination 3–6 months post-ASCT unless the patient is receiving immunomodulator therapy for active malignancy. Our observation of an increasing CRM after 5 months of ASCT among patients vaccinated only before ASCT might demonstrate the need for a booster dose following ASCT. In addition, an increase in NRM, as well as CRM, and a corresponding significant decrease in OS were observed among patients vaccinated with less than two doses.

Despite the decrease in the number of COVID-19 cases in the general population, CRM remained an important issue in patients undergoing ASCT, even after the normalization process. Strict adherence to personal protective measures and sustaining timely vaccination should never be neglected in this group of patients.

In conclusion, COVID-19 has become an important cause of mortality in the post-ASCT period. The mortality risk was higher during the 6 months following ASCT. A significant improvement in mortality and survival rates was observed in patients who received at least two doses of the vaccine. Booster doses after ASCT might have a positive impact. All patients scheduled for ASCT should be vaccinated before ASCT unless they have a clinical urgency or contraindication.

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