DOI: 10.1002/jmv.26586

LETTER TO THE EDITOR

JOURNAL OF MEDICAL VIROLOGY WILEY

Screening procedure for SARS-CoV-2 infection combining triage, nasopharyngeal swab and serological test in allogeneic stem cell transplantation recipients undergoing outpatient posttransplant follow-up

To the Editor,

In Italy, the first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive patient was identified on February 21, 2020 and as of June 30, 2020 more than 240,000 people have been diagnosed and over 34,000 have died.[1] In our country, the overall incidence of symptomatic SARS-CoV-2 infection, called coronavirus disease 2019 (COVID-19), is 396 cases every 1000 inhabitants. Our hematologic center is located in the northern-east of Italy, where this data decrease to 269 out of 1000 inhabitants (http://covid19.intelworks.io/). However, despite the availability of data on prevalence of symptomatic SARS-CoV-2 infection (COVID-19) in the general population the data on real number of asymptomatic SARS-CoV-2 carriers are unavailable.[1-4] When the first patient with COVID-19 was diagnosed in our Hospital, we were faced with the dilemma of how to counteract, in everyday clinical practice, the spread of symptomatic and asymptomatic SARS-CoV-2 infection in our allogeneic-stem cell transplant (Allo-SCT) recipients undergoing post-SCT outpatient monitoring at our day hospital ward (DH).[4]

To reduce the risk of infection spread and to minimize clinical staff exposure, Allo-SCT patients admitted to our DH strictly followed the prevention practices as recommended and published by the European group for blood and marrow transplantation (EBMT), including hygiene procedures, surgical mask and social distancing.[5] Unless necessary, caregivers were not admitted to the DH.[5,6] Before entering the DH, all Allo-SCT patients have been specifically screened in a waiting area by health care workers (using personal proctective equipment) with a triage procedure, which consisted of a questionnaire including four items to assess patients' clinical status: presence of symptoms suggestive for SARS-CoV-2 infection (such as fever >37.5°C, cough, dyspnea, headache, diarrhea, anosmia, and ageusia), and any personal possible exposure to the SARS-CoV-2 virus. In addition to the triage procedure, to further improve the SARS-CoV-2 infection screening in our Allo-SCT outpatient population, we adopted a stringent and active surveillance combining two diagnostic tests. In detail, from April, 2020 a real-time polymerase chain reaction (RT-PCR) has been performed every 7–14 days, using nasopharyngeal swab (NPS), providing results in 4-6 h and from May, 2020, one rapid serological test (Cellex qSARS-CoV-2 immunoglobilin G (IgG)/immunoglobulin M (IgM) point-of-care antibodies diagnostic rapid test) has been performed for each patient, providing results in 10 min. In the same period of time all healthcare workers were actively screened with a NPS for SARS-CoV-2 (every 14 days) and no positive cases were recorded.

Actually, the approximate sensitivity and specificity for NPS are around 70% and 95%, respectively.[7-9] Moreover, Cellex qSARS-CoV-2 IgG/IgM rapid test is a lateral flow immunoassay intended for the SARS-CoV-2 Ab qualitative detection and differentiation approved by FDA, whose declared sensitivity and specificity are 93.75% and 96.40%.

The aim of this combined approach was to identify, as early as possible, not only the symptomatic SARS-CoV-2 cases but also the asymptomatic SARS-CoV-2 carriers to avoid the spread of the viral infection between vulnerable patients and the healthcare workers and also to define the real prevalence of SARS-CoV-2 infection (including cases with or without clinical manifestations) in our high-risk immunocompromised outpatient population.

The consecutive patients who received this combined screening procedure over a 2-month period (April-May 2020) and the transplant related characteristics are reported in Table 1. Of the 70 Allo-SCT patients, 44 (63.0%) were transplanted from an unrelated donor. Forty-two (60%) were receiving immunosuppressive treatment either for prophylaxis-12 (28.5%) and for graft-versus-host disease (GVHD) treatment-30 (71.5%) and 6 patients were receiving active therapy for relapse of their underling hematologic disease. We performed a total of 185 RT-PCR tests from NPSs, with a median of 4 RT-PCR tests per patient (range: 2–7), and one rapid serological test for each patient. Taking into account that the SARS-CoV-2 epidemic peak in Italy was registered on March 20, 2020, for detecting the serological response to SARS-CoV-2 infection after an appropriate period of time from the potential virus exposure, we performed all the rapid serological test in May, 2020.

Only 8% of the triage procedures were positive for fever but none of the 70 Allo-SCT tested patients reported other symptoms potentially SARS-CoV-2 related. All the 185 RT-PCR NPS were negative. Only 1 out of 70 (1.5%) rapid serological test was positive (both IgG and IgM positive) in an asymptomatic patient 12

TABLE 1 Patients' and transplants related characteristics

Number of tested patients (2-month period)	70
Gender (M/F)	36/34
Median age, years (range)	56 (23–73)
Median time from Allo transplant, months (range)	12 (2–112)
Type of donor	
Matched unrelated	44 (63.0%)
Matched sibling	12 (17.0%)
Haploidentical	14 (20.0%)
Hematologic disease	
Acute leukemia	46 (65.5%)
Lymphoma	13 (18.5%)
Chronic myeloproliferative disease	5 (7.0%)
Myelodysplastic syndrome	4 (6.0%)
Multiple myeloma	2 (3.0%)
Previous transplant (autologous transplant)	10 (14.0%)
Ongoing immunosuppressive therapy	42 (60.0%)
Steroid or calcineurine inhibitors alone	18 (42.5%)
Calcineurine inhibitors + steroid	17 (32.5%)
Imatinib/ruxolitinib + steroid	4 (10.0%)
Extracorporeal photoapheresis + steroids	3 (7.0%)
Ongoing salvage treatment	6 (8.5%)
Chemotherapy alone	1 (16.5%)
Decitabine + donor lymphocytes infusion (DLI)	2 (33.5%)
Gilteritinib	1 (16.5%)
DLI alone	2 (33.5%)
Graft versus host disease (GVHD)	30 (43.0%)
Acute GVHD	11 (15.5%)
Chronic GVHD	19 (27.0%)
No. patients with COVID-19 symptoms	0
Nasopharyngeal swabs (NPS)	
No. of total SARS-CoV-2 NPS	185
NPS/patient, median (range)	4 (2–7)
No. of positive NPS	0
Serologic tests	
No. of SARS-CoV-2 serologic rapid test	70
No. positive SARS-CoV-2 serologic rapid test	1 (1.5%)

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

months after the unrelated Allo-SCT for a lymphoma and receiving immunosuppressive treatment for a chronic GVHD. The patient was immediately evaluated by an infectious disease team; they repeated the RT-PCR test for SARS-CoV-2 on NPS and extended it on gastric aspirate (tubage), and both were negative. Moreover, a quantitative serological test (euroimmune anti-SARS-CoV-2 Elisa) was performed, resulting negative (IgG and IgM antibodies). So that, the infectious disease team concluded for a false positive rapid serological test.

As a conclusive result of this stringent monitoring, we found that our Allo-SCT tested population was SARS-CoV-2 free (neither asymptomatic nor symptomatic cases).

Although we found no positive cases, we believe our screening experience worthy of reporting for different reasons: it represents a viable monitoring option in clinical practice in a specific setting of patients (Allo-SCT) at high risk of developing a severe SARS-CoV-2 infection.[2,5,6] Moreover, the concomitant evaluation of the two available tests (NPS and rapid serological test) might improve the detection of SARS-CoV-2 infection prevalence (we underline that the sensibility of NPS alone is around 70%) and it might be useful to verify the efficacy of the prevention practices that have been adopted according to the EBMT recommendations.[5] Last but not least, the absence of detection during the pandemic period (combining two different tests), of positive SARS-CoV-2 cases in our Allo-SCT population, represented for our patients, for their family members and also for the healthcare workers, a feeling of security. We would also underline the complete compliance of all the 70 patients for performing both the NPS and the serological test.

We are aware that, up to now, it is not completely clear which is the sensitivity and specificity of the rapid, qualitative serological SARS-CoV-2 diagnostic tests in a setting of immunocompromised patients in which a reduction of immune response and consequently of seroconversion is expected.[10-12] However, with this concern, our experience suggests that a vulnerable Allo-SCT population, if screened with a combined approach and instructed properly, might avoid the diffusion of SARS-CoV-2 infection.[5]

In conclusion, in Allo-SCT an active screening for SARS-CoV-2 infection could be performed with a combined approach, including triage procedure, molecular (RT-PCR from NPS) and serological tests. This approach could be useful to define the prevalence of SARS-CoV-2 infection (including symptomatic and asymptomatic cases) in the context of a vulnerable population and it should be taken into account as a useful tool especially in the case of a regrowth of SARS-CoV-2 virus spread.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Anna Candoni, Alessandra Sperotto, and Giuseppe Petruzzellis: data collection, data analysis and drafting the manuscript. Renato Fanin: data collection. Francesca Patriarca: support in study design. Carlo Tascini and Renato Fanin: study design and manuscript revision.

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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