

Rapid Antibody Testing for SARS-CoV-2 in Asymptomatic and Paucisymptomatic Healthcare Professionals in Hematology and Oncology Units Identifies Undiagnosed Infections

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The emergence of coronavirus disease 2019 (COVID-19) represents a major threat for cancer patients and healthcare professionals. The huge numbers of infected patients globally and the continuous increase of newly diagnosed cases pose an unprecedented challenge to healthcare systems.¹ The reasons for the widespread and rapid transmission of the infection are not completely certain and are provoking changes in public health recommendations as well as anxieties. Most patients in Hematology and Oncology (Hemat-Onc) units are immune-compromised because of cancer and cytotoxic treatments and are at high risk of developing life-threatening infections.² In addition, an infected patient must delay treatment with potentially dangerous consequences.³

During the beginning of COVID-19 pandemic in Italy, the lack of meticulous contact tracing, the crowded emergency rooms, the shortage of personal protective equipments as well as the time required to set up hospital areas exclusively dedicated to COVID-19 patients, contributed to virus spreading. Within the hospitals, the Hemat-Onc units have been soon identified as COVID-free areas because of the patients' frailty. The safety of patients and healthcare workers should have been a priority, but the dramatic emergency shifted all the efforts to critically ill patients more than producing comprehensive guidelines for the various hospital specialties. As a result, in the peculiar situation of hematologic malignancy patients, the regular testing by nasopharyngeal swabs before chemo-immunotherapy has been recommended by the scientific societies weeks before the health authorities.

Despite some of the measures indicated from the authorities to prevent contagion spreading (hand washing with sanitizer, surgical mask wearing, patient isolation, gown) are traditionally applied in Hemat-Onc units to prevent infections in neutropenic patients, viral shedding by asymptomatic or paucisymptomatic people represents a serious threat as a sizeable fraction of COVID-19 infections go undiagnosed.

Thus, considering that the large-scale use of nasopharyngeal swabs (NPS) is not realistic because of the limited testing capacities, the health authority discussion is now focused on the role of antibody testing to protect patients and workers to limit the risk of healthcare-associated infections. Under the hypothesis that serological testing for COVID-19 might be used to identify possible infected individuals, we conducted the first prospective study to evaluate the prevalence of seropositivity in asymptomatic or paucisymptomatic Hemat-Onc professionals.

At the Milano National Cancer Institute, Hemat-Onc doctors, nurses, paramedics and staff members were tested during the April 2020 pandemic peak. According to the presence of symptoms (rhinorrhea, pharyngitis, myalgia, fatigue, headache, anosmia, dysgeusia, nausea, diarrhea, cough, fever, dyspnea) in the previous 14 days, they were categorized as asymptomatic, paucisymptomatic (no fever and cough or dyspnea), and symptomatic. Participants gave informed consent and the protocol was approved by Ethics Committee. We used a COVID-19 rapid immunochromatographic test for determination of antibodies in whole blood (PRIMA LAB SA, Switzerland) reported to have 98% specificity, 100% sensitivity, 98.6% accuracy for IgG and 96% specificity, 85% sensitivity, 92.9% accuracy for IgM. The presence of viral RNA was searched by reverse transcription polymerase chain reaction (RT-PCR) in NPS of seropositive cases only. Differences in the proportion of positive serological tests were assessed by Fisher exact test.

Twelve known symptomatic workers with a previously confirmed diagnosis of COVID-19 by RT-PCR of SARS-CoV-2 RNA in NPS, served as positive controls: 10 were IgG positive only (IgG+), 2 had IgG and IgM (IgM+/IgG). In this study, 234 asymptomatic or paucisymptomatic subjects were tested twice over a 2-week period of time as serology sensitivity is over 90% within 12 days after infection onset.⁴ Eleven of 194 (5.7%) asymptomatic workers were found to be positive: 7 were positive for IgG (IgG+) and 4 for IgM (IgM+). Among the seropositives, 4

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Table 1**Antibody Testing on Asymptomatic and Paucisymptomatic Healthcare Professionals.**

Results of First Round Testing ^a (N = 234)		
Gender (male/female)		66/168
Age, years (median)		43
Medical Doctors (N = 101): 79 asymptomatic and 22 paucisymptomatic		
Total positives: 7/101 (6.9%)		
IgG positive	7	3 asymptomatic, 4 paucisymptomatic
IgM positive	0	-
IgG and IgM positive	0	-
NPS positive/negative	3/4	2 asymptomatic, 1 paucisymptomatic
Nurses/Paramedics/staff members (N = 133): 114 asymptomatic and 19 paucisymptomatic		
Total positives: 15/133 (11.3%)		
IgG positive	10	4 asymptomatic, 6 paucisymptomatic
IgM positive	4	asymptomatics
IgG and IgM positive	1	paucisymptomatic
NPS positive/negative	4/11	2 asymptomatic, 2 paucisymptomatics

^aTotal positive 22 out of 234 (9.4%); NPS: nasopharyngeal swabs.

of the 7 IgG+ tested positive when the viral RNA was amplified in their NPS. In addition, 11 of 40 (27.5%) paucisymptomatic workers were found to be positive: 10 IgG+ (2 with a concomitant positive NPS) and 1 IgM+/IgG+ with a positive NPS (Table 1). Most frequent symptoms were: anosmia (5), rhinorrhea (5), dysgeusia (4) and headache (4).

After 10 to 14 days, 204 subjects underwent a second round of testing and all results were confirmed, except for 2 IgM cases who were previously positive and now tested negative. In addition, 3 more asymptomatic workers became seropositive (2 IgG+ and 1 IgM+). These data indicate that the situation can change and that repeated testing can reveal false IgM positives, but also new occult infections.

Seropositivity rates were similar in all professional categories tested (doctors, nurses, paramedics or staff members). The percentage of seropositives was not higher in out-patient facilities (day-hospital and supportive care units) as compared to the in-patient wards. Total number of healthcare workers with documented diagnosis of COVID-19, since March 2020 in the Hemat-Onc units, was 12, although we are aware of possible underestimations as additional workers during this period, were left at home with influenza-like symptoms as a precautionary measure and underwent NPS only immediately before the readmission to work to certify their negativity. Thus collectively, considering a total of 246 Hemat-Onc workers, the estimate of infected by SARS-CoV-2 was 35 (14.2% of which 23 asymptomatic/paucisymptomatic and 12 symptomatic).

The existence of undocumented, but infectious cases is critical for the spread of any respiratory virus. COVID-19 often produces mild, or no symptoms, go undiagnosed and this is particularly dangerous in the hospital setting. These undocumented infections have facilitated the epidemic in Wuhan and probably also in Lombardy.^{5,6} A recent report on 28 cancer patients with COVID-19 indicates that 53.6% of them developed severe events and 28.6% died.² Very preliminary data from the Italian Society of Hematology suggest that also in the hematology and bone marrow transplantation setting, mortality for COVID-19 infected patients, seems at least 30% (unpublished data). Thus stringent control measures in Hemat-Onc units are of utmost importance to keep them COVID-free.⁷ For this reason, patients receiving chemo-immunotherapy or transplants are now regularly tested by NPS, but a standard approach to screen healthcare workers is not formally in place yet. To evaluate the prevalence

and to give a picture of occult infections in a hospital setting, we studied the serologic status of asymptomatic and paucisymptomatic workers. The rationale was that they represent a potential reservoir for in-hospital transmission of COVID-19.

Many serology tests for the SARS-CoV-2 are under development and authorities have not decided yet which test should be used at the national level. It is already clear that these tests could provide useful information for the decision making concerning the public health. Accordingly, we have shown that the prevalence of asymptomatic/paucisymptomatic healthcare workers in the Hemat-Onc Units at the Milano National Cancer Institute with a positive serology is 9.4% and that 31.8% of them had a confirmed diagnosis of COVID-19 by RT-PCR of SARS-CoV-2 RNA in NPS. These undocumented cases were likely to represent a real threat for patients, colleagues and also family contacts. Seropositivity was more frequent in the paucisymptomatic cohort (27.5% vs 5.7%, $p < 0.002$). Our data indicate that even mild symptoms can herald a potentially infectious worker. Seropositive subjects should be strictly monitored, undergo NPS test and household quarantined when positive.⁸

In conclusion, our study has several practical implications: (1) the prevalence of occult infections is not negligible in Hemat-Onc workers and it is similar to the general Italian population; (2) the screening with repeated serologic testing allows the identification of occult infected workers even when they are only IgG seropositives and limits the use of NPS; (3) both asymptomatic and paucisymptomatic workers can be potentially infectious and contribute to COVID-19 transmission.

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