bjh short report

COVID-19 elicits an impaired antibody response against SARS-CoV-2 in patients with haematological malignancies

Francesco Passamonti,[1,2] Alessandra Romano,[3] Marco Salvini,[2] Francesco Merli,[4] Matteo G. Della Porta,[5] Riccardo Bruna,[6] Elisa Coviello,[7] Ilaria Romano,[8] Roberto Cairoli,[9] Roberto Lemoli,[10] Francesca Farina,[11] Adriano Venditti,[12] Alessandro Busca,[13] Marco Ladetto,[14] Massimo Massaia,[15] Antonio Pinto,[16] Luca Arcaini,[17] Agostino Tafuri,[18] Francesco Marchesi,[19] Nicola Fracchiolla,[20] Monica Bocchia,[21] Daniele Armiento,[22] Anna Candoni,[23] Mauro Krampera,[24] Mario Luppi,[25] Valeria Cardinali,[26] Sara Galimberti,[27] Chiara Cattaneo,[28] Elettra Ortu La Barbera,[29] Roberto Mina,[30] Francesco Lanza,[31] Giuseppe Visani,[32] Pellegrino Musto,[33] Luigi Petrucci,[34] Francesco Zaja,[35] Paolo A. Grossi,[1,2] Lorenza Bertù,[2] Livio Pagano,[36] Paolo Corradini[37] and on behalf of the ITA-HEMA-COV Investigators*

[1]Dipartimento di Medicina e Chirurgia, Università dell'Insubria, [2]ASST Sette Laghi, Ospedale di Circolo of Varese, Varese, [3]Università degli Studi di Catania, Catania, [4]Hematology, AUSL-IRCCS, Reggio Emilia, [5]Department of Biomedical Sciences, Humanitas Clinical and Research Hospital – IRCCS, Humanitas University, Milano, [6]Department of Translational Medicine, University of Eastern Piedmont and Ospedale Maggiore della Carità, Novara, [7]Ospedale Policlinico San Martino-IRCCS, Genova, [8]University of Florence and AOU Careggi, Firenze, [9]ASST Grande Ospedale Metropolitano Niguarda, Milano, [10]University of Genoa, Genova, [11]San Raffaele, Scientific Institute, Milano, [12]Ematologia, Dipartimento di Biomedicina

Summary

COVID-19 is associated with high mortality in patients with haematological malignancies (HM) and rate of seroconversion is unknown. The ITA-HEMA-COV project (NCT04352556) investigated patterns of seroconversion for SARS-CoV-2 IgG in patients with HMs. A total of 237 patients, SARS-CoV-2 PCR-positive with at least one SARS-CoV-2 IgG test performed during their care, entered the analysis. Among these, 62 (26·2%) had myeloid, 121 (51·1%) lymphoid and 54 (22·8%) plasma cell neoplasms. Overall, 69% of patients (164 of 237) had detectable IgG SARS-CoV-2 serum antibodies. Serologically negative patients (31%, 73 of 237) were evenly distributed across patients with myeloid, lymphoid and plasma cell neoplasms. In the multivariable logistic regression, chemoimmunotherapy [odds ratio (OR), 3·42; 95% confidence interval (CI), 1·04–11·21; $P = 0·04$] was associated with a lower rate of seroconversion. This effect did not decline after 180 days from treatment withdrawal (OR, 0·35; 95% CI: 0·11–1·13; $P = 0·08$). This study demonstrates a low rate of seroconversion in HM patients and indicates that treatment-mediated immune dysfunction is the main driver. As a consequence, we expect a low rate of seroconversion after vaccination and thus we suggest testing the efficacy of seroconversion in HM patients.

Keywords: Covid-19, SARS-CoV-2, leukemia, lymphoma, myeloma.

 British Journal of Haematology, 2021, **195,** 371–377

First published online 16 July 2021
doi: 10.1111/bjh.17704

e Prevenzione, Università Tor Vergata, Roma, [13]*Stem Cell Transplant Center, AOU Citta' della Salute e della Scienza of Torino, Torino,* [14]*Dip di Medicina Traslazionale, Università del Piemonte Orientale ed AO SS Antonio e Biagio e Cesare Arrigo, Alessandria,* [15]*Santa Croce Hospital, Cuneo,* [16]*Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Napoli,* [17]*Division of Hematology, Department of Molecular Medicine, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia,* [18]*Department of Clinical and Molecular Medicine, Sapienza, University Hospital Sant'Andrea, University of Rome, Roma,* [19]*Hematology and Stem Cell Transplant Unit, IRCCS Regina Elena National Cancer Institute, Rome,* [20]*Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Milan,* [21]*Azienda Ospedaliera Universitaria Senese, University of Siena, Siena,* [22]*Unit of Hematology, Stem Cell Transplantation, University Campus Bio-Medico, Rome,* [23]*Division of Hematology, University Hospital of Udine -ASUFC, Udine,* [24]*Department of Medicine, University of Verona, Verona,* [25]*Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena,* [26]*University of Perugia, Perugia,* [27]*Università di Pisa, Pisa,* [28]*ASST*-Spedali Civili, Brescia, [29]*Ospedale Santa Maria Goretti, Latina,* [30]*Università di Torino, Azienda Ospedaliera Città della Salute e della Scienza, Alessandria,* [31]*Santa Maria delle Croci, Ravenna,* [32]*Azienda Ospedaliera Ospedali Riuniti Marche Nord, Pesaro,* [33]*Department of Emergency and Organ Transplantation, Unit of Hematology and Stem Cell Transplantation, "Aldo Moro" University School of Medicine, AOU Consorziale Policlinico, Bari,* [34]*Division of Hematology, Department of Translational and Precison Medicine, Sapienza University of Rome, Rome,* [35]*Università di Trieste, Trieste,* [36]*University Cattolica del Sacro Cuore, Roma, and* [37]*University of Milan, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy*

Received 25 May 2021; accepted for publication 25 June 2021

Correspondence: Francesco Passamonti, Hematology, Department of Medicine and Surgery, University of Insubria, Via Guicciardini, 21100, Varese, Italy.
E-mail: francesco.passamonti@uninsubria.it

*A list of the ITA-HEMA-COV Investigators is available after the Acknowledgement section.

Introduction

COVID-19, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been declared pandemic in March 2020. According to the largest series, its mortality for patients with haematological malignancies (HM) was 37%.[1,2] A meta-analysis including 3 210 HMs reported an overall 34% risk of death.[2] Among 650 patients with multiple myeloma (MM),[3] 198 with chronic lymphocytic leukaemia (CLL),[4] 177 with non-Hodgkin lymphomas (NHL),[5] and 318 who received haematopoietic stem cell transplantation (HSCT)[6] case fatality was 33%, 33%, 34%, and 33%, respectively.

Several studies have shown that 95–100% of immunocompetent patients with COVID-19 have seroconverted about three weeks after symptom onset,[7,8] while this information in patients with HM is scant. A low rate (67%) of anti-SARS-CoV-2 IgG development has been described in 21 patients with CLL (67%);[9] a slightly better rate (88%) was found in eight patient with acute myeloid leukaemia.[10]

This study was registered in the ClinicalTrials.gov Identifier, NCT04352556. We investigated patterns of seroconversion for SARS-CoV-2 IgG in a broad range of patients with HMs. The is a retrospective study and the cohort came from the Italian Hematology Alliance on COVID-19 (ITA-HEMA-COV) project, that already provided information on mortality in HM with COVID-19.[1] Addressing the rate of humoral immune response to SARS-CoV-2 in HM patients who have been exposed to SARS-CoV-2 is a critical step to properly inform and develop vaccination strategies and monitoring in this vulnerable patient population. In fact, there is preliminary evidence showing a low rate of seroconversion after vaccines against SARS-CoV-2.[11]

Methods

To investigate the presence of SARS-CoV-2 antibodies, we analyzed serology reports within the ITA-HEMA-COV database, starting 23 February 2020, until 17 February 2021 (first and last observed HM patient with COVID-19). The study was approved by the institutional review board of each centre. A total of 2 463 patients (735 myeloid, 1 214 lymphoid, 514 plasma cell neoplasms) were identified with a real-time polymerase chain reaction (RT-PCR) positive for SARS-CoV-2. We excluded 577 cases who died without performing serology and 1 649 coming from centres without test availability. Eventually, 237 patients with HM, SARS-CoV-2 PCR-positive and at least one SARS-CoV-2 IgG test performed during their standard care, were included. For SARS-CoV-2 serological testing we used commercial, widely available high-throughput immunoassays available at the centres such as the Abbott (SARS-CoV-2 nucleocapsid IgG, Chicago, IL, USA), the DiaSorin (SARS-CoV-2 Spike-1 and Spike-2 IgG, Saluggia, Italy), the Roche [SARS-CoV-2 nucleocapsid and Spike protein RBD (receptor-binding-domain) IgG, Basel, Switzerland] or the Siemens (Atellica, SARS-CoV-2 Spike protein RBD IgG, Munich, Germany) tests. Sensitivity and specificity of these tests was at least 98% in a head-to-head comparison study,[12] with some divergent results in seroprevalence studies on cancer patients.[13]

Continuous variables are expressed as median, minimum, and maximum values. Categorical variables are presented as frequencies and percentages. Characteristics of the study population were described for patients with a positive result to the SARS-CoV-2 IgG test and for negative ones.

Univariate logistic regression models were applied to study the association between the absence of seroconversion and the following variables: age, sex, comorbidities, HM type, COVID-19 disease severity, hospitalization, last therapy applied and time to COVID-19, active therapy (time from last therapy to COVID-19 within three months) and time from COVID-19 to first serology evaluation. A multivariable logistic regression model, adjusted for the time from COVID-19 to first serology evaluation, was implemented using parameters of interest. In addition, we did this latter analysis on the subgroup on active therapy. The odds ratio (OR) together with the 95% confidence interval (CI) and Wald chi-square *P*-value were calculated. All statistical analyses were done with SAS version 9.4 and R statistical software version 3.2.0 (Cary, NC, USA).

Results and discussion

A total of 237 patients were evaluated: 62 (26·2%) had myeloid neoplasms, 121 (51·1%) lymphoid neoplasms, and 54 (22·8%) had plasma cell neoplasms. As the distribution of HMs was superimposable to that of the whole series of 2 463 cases ($P = 0{\cdot}40$), findings obtained here can be representative of a real-life situation. Median age was 61 years (range, 19–91), male/female ratio was 1·14, with most patients having symptomatic COVID-19 (78·5%). A detailed description of patients and HMs is available in Table I.

Table I. Characteristics of 237 patients with haematological malignancies, exposed to SARS-CoV-2 infection according to IgG serology response.

	Positive serology n = 164	Negative serology n = 73	All patients n = 237
Age, years			
Median [min–max]	61 [19–91]	61 [22–88]	61 [19–91]
Sex, *n* (%)			
Female	75 (45·73)	36 (49·32)	111 (46·84)
Charlson comorbidity Index			
Median [min–max]	3 [0–14]	4 [0–13]	3 [0–14]
Coexisting condition, *n* (%)			
Heart disease	16 (9·76)	9 (12·33)	25 (10·55)
Pulmonary disease	15 (9·15)	6 (8·22)	21 (8·86)
Vascular disease	19 (11·59)	4 (5·48)	23 (9·70)
Connective tissue disease	5 (3·05)	3 (4·11)	8 (3·38)
Liver disease	3 (1·83)	3 (4·11)	6 (2·53)
Kidney disease	5 (3·05)	3 (4·11)	8 (3·38)
Diabetes	5 (6·85)	13 (7·93)	18 (7·59)
Non-haematological cancer	13 (7·93)	7 (9·59)	20 (8·44)
Type of haematological malignancies, *n* (%)	47 (28·66)	15 (20·55)	62 (26·16)
Myeloid neoplasms	14 (8·54)	4 (5·48)	18 (7·59)
Myeloproliferative neoplasm	9 (5·49)	0 (0·00)	9 (3·80)
Myelodysplastic syndrome	21 (12·80)	10 (13·70)	31 (13·08)
Acute myeloid leukaemia	3 (1·83)	1 (1·37)	4 (1·69)
Acute lymphoblastic leukaemia	4 (2·44)	2 (2·74)	6 (2·53)
Lymphomas	71 (43·29)	44 (60·27)	115 (48·52)
Hodgkin lymphomas	14 (8·5%)	1 (1·4)	15 (6·3)
Aggressive non-Hodgkin lymphomas	21 (12·80)	24 (32·88)	45 (18·99)
Indolent non-Hodgkin lymphomas	14 (8·54)	15 (20·55)	29 (12·24)
Chronic lymphoproliferative disorders	21 (12·80)	4 (5·48)	25 (10·55)
Plasma cell neoplasms	42 (25·61)	12 (16·44)	54 (22·78)
Plasma cell myeloma	33 (20·12)	11 (15·07)	44 (18·57)
Symptomatic, *n* (%)			
Yes	52 (71·23)	134 (81·71)	186 (78·48)
COVID-19 disease severity, *n* (%)			
Mild	78 (47·56)	32 (43·84)	110 (46·41)
Severe	51 (31·10)	19 (26·03)	70 (29·54)
Critical	5 (3·05)	1 (1·37)	6 (2·53)
Asymptomatic	30 (18·29)	21 (28·77)	51 (21·52)
Last therapy type, *n* (%)			
Chemotherapy	47 (28·66)	15 (20·55)	62 (26·16)
Immunotherapy	7 (4·27)	8 (10·96)	15 (6·33)
Chemoimmunotherapy	28 (17·07)	26 (35·62)	54 (22·78)
Targeted therapy	33 (20·12)	13 (17·81)	46 (19·41)
Autologous stem cell transplant	10 (6·10)	1 (1·37)	11 (4·64)
Allogeneic stem cell transplant	6 (3·66)	3 (4·11)	9 (3·80)
Active therapy, *n* (%)	85 (51·83)	48 (65·75)	133 (56·12)
Hospitalized patients, *n* (%)	44 (60·27)	90 (54·88)	134 (56·54)
Time from COVID-19 to first serology, days			
Median [min–max]	34 [2–275]	46 [7–383]	38 [2–383]
Time from last therapy to COVID-19, days			
Median [min–max]	49 [1–3 566]	27 [1–2 628]	42 [1–3 566]

Most patients (83·1%, 197 of 237) received HM-directed therapies before COVID-19. In detail, it was chemotherapy in 62 (26·2%), chemoimmunotherapy in 54 (22·8%), immunotherapy only in 15 (6·3%), targeted therapies in 46 (19·4%), autologous and allogeneic HSCT in 11 (4·6%) and 9 (3·8%) respectively. Among these, 133 (56%) were on active therapy at the time of COVID-19.

Overall, 69% of patients (164 of 237) tested positive for IgG SARS-CoV-2 antibodies and 31% (73 of 237) negative. This indicates that one-third of patients with HM are at high risk of failing seroconversion which, contrarily, approaches 100% in the general population.[7] The median time from COVID-19 to first SARS-CoV-2 IgG serology evaluation was 38 days (range, 2–383), longer than that reported

in the immunocompetent population.[7] In fact, viral shedding is persistent in immunocompromised patients[14] and, as a consequence, seroconversion comes later. Testing frequencies in IgG-positive and IgG-negative cases is reported in Fig 1A: finding patients without seroconversion tested later (OR, 1·01; 95% CI, 1·00–1·01; $P = 0·02$) corroborates these results. Figure S1 reports the timing of seroconversion in seven patients who resulted negative in an early SARS-CoV-2 IgG evaluation and subsequently became positive. This suggests that measuring serological response too soon after SARS-CoV-2 infection in HM might lead to an incorrect evaluation of immune response. This probably explains the very low rate of seroconversion reported in 20 HMs (16·6%), tested after 12 days from COVID-19.[15]

Figure 1B shows the rate of seroconversion per HM type and specific treatments (more details in Figure S2). We found that serological non-responders were spread evenly across patients with lymphomas, MM and myeloid neoplasms. However, the univariate logistic regression (Table SI) showed that patients with absent seroconversion more likely had lymphoid neoplasms (OR, 2·15; 95% CI, 1·03–4·50; $P = 0·04$), received chemoimmunotherapy (OR, 6·68, 95% CI, 2·22–20·08; $P = 0·0007$), immunotherapy (OR, 4·71; 95% CI, 1·07–20·79; $P = 0·04$), or were on active therapy at the time of COVID-19 (OR, 1·84; 95% CI, 1·03–3·27, $P = 0·04$). To note, 27 out of 57 (47·4%) patients receiving immunotherapy/chemoimmunotherapy within one year from COVID-19 resulted positive.

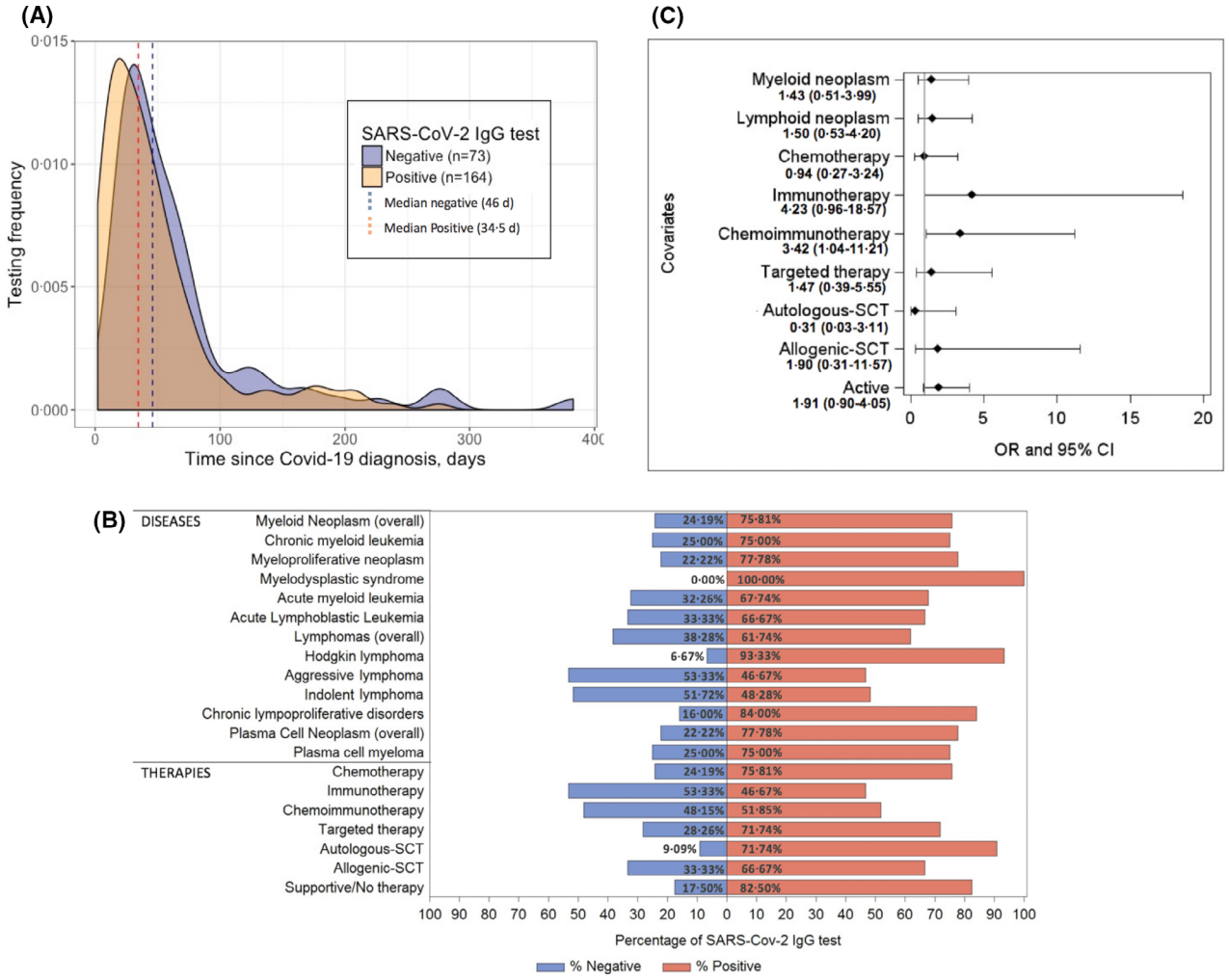

Fig 1. (A) Timing and antibody testing after a positive real-time polymerase chain reaction (RT-PCR) test. The testing frequency of patients evaluated showed that those resulting IgG-negative have been tested later (46 days), than positive (34 days) and some patients were IgG-positive long time after COVID-19 diagnosis. (B) Rate of seroconversion according to haematological malignancy and treatment. Serological non-responders were spread evenly across patients with myeloid, lymphoid and plasma cell neoplasms. Percentages of serological non-responders and responders are reported. (C) Results of multivariable analysis for identification of factors affecting negative seroconversion for SARS-CoV-2 in patients with haematological malignancies. Multivariable logistic regression revealed that chemoimmunotherapy ($P = 0·04$) and immunotherapy ($P = 0·06$) were associated with a significant and borderline lower rate of seroconversion, respectively. OR values with 95% CI are reported. Plasma cell neoplasms and no therapy represent the reference for the analysis. SCT, stem cell transplantation; OR, odds ratio; CI, confidence interval. [Colour figure can be viewed at wileyonlinelibrary.com]

In the multivariable logistic regression on the whole cohort, chemoimmunotherapy (OR, 3·42; 95% CI, 1·04–11·21; $P = 0.04$) was associated with a significantly lower rate of seroconversion, while immunotherapy (OR, 4·23; 95% CI, 0·96–18·57; $P = 0·06$) was of borderline significance (Fig 1C).

When analyzing patients on active therapy, chemoimmunotherapy (OR, 8·02; 95% CI, 2·25–28·56; $P = 0·001$), immunotherapy (OR, 5·89; 95% CI, 1·19–29·26; $P = 0·03$) and targeted therapy (OR, 3·61; 95% CI, 1·07–12·18; $P = 0·04$) were independent predictors of lower seroconversion (Figure S3). Both analyses maintained their value even adjusting for the time from COVID-19 to serology. In addition, the effect of chemoimmunotherapy and immunotherapy did not decline after 180 days from treatment withdrawal (OR, 0·35; 95% CI, 0·11–1·13; $P = 0·08$).

Conclusions

In conclusion, this study shows that COVID-19 can elicit antibodies to SARS-CoV-2 in 69% of patients with HM. The mechanism for this reduced seroconversion is not fully known, but our study indicates that treatment-mediated immune dysfunction can play an important role. Limitations of the study come from the real-world data collection, i.e. various SARS-CoV-2 lgG tests used with different epitopes and different thresholds for seroconversion, and various time points for blood sampling. Then, it should be noted that the cellular response to the SARS-CoV-2 may also have a protective role in HM patients who have recovered from COVID-19 but failed humoral response. We expect a lower rate of seroconversion after vaccination and thus HM patients should be tested for seroconversion and should maintain all the protective measures. Our data further highlight the importance of vaccination for caregivers and the need for effective infection treatment. HM can potentially become a reservoir for viral genetic variants.

Acknowledgements

We thank Dr Roberta Mattarucchi and Dr Alessia Ingrassia from the Clinical Trial Center of the A.S.S.T. and Sette Laghi of Varese for managing the study protocol and procedures across many Institutional Review Boards. The list of ITA-HEMA-COV members is reported below: all provided and analyzed data. Open Access Funding provided by Universita degli Studi dell'Insubria within the CRUI-CARE Agreement. [Correction added on 26 May 2022, after first online publication: CRUI funding statement has been added.]

List of ITA-HEMA-COV investigators

Francesco Passamonti,[1,2] Alessandra Romano,[3] Marco Salvini,[2] Francesco Merli,[4] Matteo Giovanni Della Porta,[5] Riccardo Bruna,[6] Elisa Coviello,[7] Ilaria Romano,[8] Roberto Cairoli,[9] Roberto Lemoli,[10] Francesca Farina,[11] Adriano Venditti,[12] Alessandro Busca,[13] Marco Ladetto,[14] Massimo Massaia,[15] Antonio Pinto,[16] Luca Arcaini,[17] Agostino Tafuri,[18] Francesco Marchesi,[19] Nicola Fracchiolla,[20] Monica Bocchia,[21] Daniele Armiento,[22] Anna Candoni,[23] Mauro Krampera,[24] Mario Luppi,[25] Valeria Cardinali[26] Sara Galimberti,[27] Chiara Cattaneo,[28] Elettra Ortu La Barbera,[29] Roberto Mina,[30] Francesco Lanza,[31] Giuseppe Visani,[32] Pellegrino Musto,[33] Luigi Petrucci,[34] Francesco Zaja,[35] Enrico Derenzini,[36] Monia Marchetti,[37] Anna M. Scattolin,[38] Alessandro Corso,[39] Patrizia Tosi,[40] Filippo Gherlinzoni,[41] Carlo G. Passerini,[42] Michele Cavo,[43] Carmen Fava,[44] Mauro Turrini,[45] Carlo Visco,[24] Paolo Antonio Grossi,[1,2] Lorenza Bertù,[2] Livio Pagano,[46] Patrizia Zappasodi[17], Michele Merli,[2] Barbara Mora,[1,2] Alessandro M. Vannucchi[8] and Paolo Corradini.[47]

Affiliation of ITA-HEMA-COV investigators

[1]Dipartimento di Medicina e Chirurgia, Università dell'Insubria, Italy; [2]ASST Sette Laghi, Ospedale di Circolo of Varese, Italy; [3]Università degli Studi di Catania, Catania, Italy; [4]Hematology, AUSL-IRCCS, Reggio Emilia, Italy; [5]Humanitas Clinical and Research Hospital – IRCCS and Department of Biomedical Sciences, Humanitas University, Milan, Italy; [6]Department of Translational Medicine, University of Eastern Piedmont and Ospedale Maggiore della Carità, Novara, Italy; [7]Ospedale Policlinico San Martino-IRCCS, Genoa, Italy; [8]University of Florence and AOU Careggi, Florence , Italy; [9]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [10]University of Genoa, Genoa, Italy; [11]San Raffaele, Scientific Institute, Milan, Italy; [12]Ematologia, Dipartimento di Biomedicina e Prevenzione, Università Tor Vergata, Rome, Italy; [13]Stem Cell Transplant Center, AOU Citta' della Salute e della Scienza of Turin, Italy; [14]Dip di Medicina Traslazionale, Università del Piemonte Orientale ed AO SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; [15]Santa Croce Hospital, Cuneo, Italy; [16]Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; [17]Division of Hematology, Fondazione IRCCS Policlinico San Matteo & Department of Molecular Medicine, University of Pavia, Italy; [18]University Hospital Sant'Andrea, Department of Clinical and Molecular Medicine, Sapienza, Univ. of Rome, Rome, Italy; [19]Hematology and Stem Cell Transplant Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy; [20]Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy; [21]Azienda Ospedaliera Universitaria Senese, University of Siena, Italy; [22]Unit of Hematology, Stem Cell Transplantation, University Campus Bio-Medico, Rome, Italy; [23]Division of Hematology, University Hospital of Udine - ASUFC, Udine, Italy; [24]Department of Medicine, University of Verona, Italy; [25]Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy; [26]University of Perugia, Italy; [27]Università di Pisa, Pisa, Italy; [28]ASST-Spedali Civili, Brescia, Italy; [29]Ospedale Santa Maria Goretti, Latina, Italy; [30]Università di Torino, Azienda Ospedaliera Città della Salute e della Scienza, Turin, Italy;

[31]Santa Maria delle Croci, Ravenna, Italy; [32]Azienda Ospedaliera Ospedali Riuniti Marche Nord, Pesaro, Italy; [33]Department of Emergency and Organ Transplantation,"Aldo Moro" University School of Medicine and Unit of Hematology and Stem Cell Transplantation, AOU Consorziale Policlinico, Bari, Italy; [34]Division of Hematology Department of Translational and Precison Medicine, Sapienza University of Rome, Italy; [35]Università di Trieste, Trieste, Italy; [36]Oncohematology Division, IEO European Institute of Oncology IRCCS, Milan, Italy; Department of Health Sciences, University of Milan, Italy; [37]Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; [38]Ospedale dell'Angelo di Mestre, Mestre, Italy; [39]ASST Ovest Milanese, Legnano, Italy; [40]Ospedale degli Infermi di Rimini, Rimini, Italy; [41]Ospedale Ca' Foncello, Vicenza, Italy; [42]Università degli Studi di Milano-Bicocca, Italy; [43]IRCCS Azienda Ospedaliero-Universitaria, Bologna, Italy e Istituto di Ematologia "Seràgnoli", Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università degli Studi, Bologna, Italy; [44]University of Turin, Turin, Italy; [45]Ospedale Valduce, Como, Italy; [46]University Cattolica del Sacro Cuore, Rome, Italy; [47]University of Milan & Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

Funding information

The study has been supported by the charity AIL (Associazione italiana contro le leucemie-linfomi e mieloma) Onlus of Varese, by grants from the Ministero della Salute, Rome, Italy (Finalizzata 2018, NET-2018-12365935, Personalized medicine program on myeloid neoplasms: characterization of the patient's genome for clinical decision making and systematic collection of real world data to improve quality of health care), by grants from the Ministero dell'Istruzione, dell'Università e della Ricerca, Roma, Italy (PRIN 2017, 2017WXR7ZT; Myeloid Neoplasms: an integrated clinical, molecular and therapeutic approach) and by grants from Fondazione Matarelli, Milan.

Author contributions

FP designed and performed the research, analyzed data, and wrote the paper; PC designed the research, analyzed data, and wrote the paper; MS and PAG designed the research; LB did statistical analysis; AR, FM, MGD, RB, EA, IR, RC, RL, FF, AV, AB, ML, MM, AP and LA provided and analyzed data.

Conflict of interest

The authors have no conflicts of interest to disclose.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supplemental data.

Table SI. Results of univariate logistic regression for identification of factors affecting negative seroconversion for SARS-CoV-2 in haematological malignancies.

Fig S1. Description of seroconversion time period in seven patients with haematological malignancies.

Fig S2. Rate of seroconversion in haematological malignancies according to detailed treatments.

Fig S3. Results of multivariable analysis for identification of factors affecting negative seroconversion for SARS-CoV-2 in patients with haematological malignancies on active therapy.

References

1. Passamonti F, Cattaneo C, Arcaini L, Bruna R, Cavo M, Merli F, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. *Lancet Haematol*. 2020;**7**(10):e737–45.
2. Vijenthira A, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood*. 2020;**136**(25):2881–92.
3. Chari A, Samur MK, Martinez-Lopez J, Cook G, Biran N, Yong K, et al. Clinical features associated with COVID-19 outcome in multiple myeloma: first results from the International Myeloma Society data set. *Blood*. 2020;**136**(26):3033–40.
4. Mato AR, Roeker LE, Lamanna N, Allan JN, Leslie L, Pagel JM, et al. Outcomes of COVID-19 in patients with CLL: a multicenter international experience. *Blood*. 2020;**136**(10):1134–43.
5. Regalado-Artamendi I, Jiménez-Ubieto A, Hernández-Rivas JÁ, Navarro B, Núñez L, Alaez C, et al. Risk factors and mortality of COVID-19 in patients with lymphoma: a multicenter study. *Hemasphere*. 2021;**5**(3):e538.
6. Sharma A, Bhatt NS, St Martin A, Abid MB, Bloomquist J, Chemaly RF, et al. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study. *Lancet Haematol*. 2021;**8**(3):e185–93.
7. Long Q-X, Liu B-Z, Deng H-J, Wu G-C, Deng K, Chen Y-K, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nat Med*. 2020;**26**(6):845–8.
8. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients with novel coronavirus disease 2019. *Clin Infect Dis*. 2020;**71**(16):2027–34.
9. Roeker LE, Knorr DA, Pessin MS, Ramanathan LV, Thompson MC, Leslie LA, et al. Anti-SARS-CoV-2 antibody response in patients with chronic lymphocytic leukemia. *Leukemia*. 2020;**34**(11):3047–9.
10. O'Nions J, Muir L, Zheng J, Rees-Spear C, Rosa A, Roustan C, et al. SARS-CoV-2 antibody responses in patients with acute leukaemia. *Leukemia*. 2021;**35**(1):289–92.
11. Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood*. 2021;**137**(23):3165–73.
12. Ainsworth M, Andersson M, Auckland K, Baillie JK, Barnes E, Beer S, et al. Performance characteristics of five immunoassays for SARS-CoV-2: a head-to-head benchmark comparison. *Lancet Infect Dis*. 2020;**20**(12):1390–400.
13. van Dam P, Huizing M, Roelant E, Hotterbeekx AN, De Winter FHR, Kumar-Singh S, et al. Immunoglobin G/total antibody testing for SARS-CoV-2: a prospective cohort study of ambulatory patients and health care workers in two Belgian oncology units comparing three commercial tests. *Eur J Cancer*. 2021;**148**:328–39.
14. Aydillo T, Gonzalez-Reiche AS, Aslam S, van de Guchte A, Khan Z, Obla A, et al. Shedding of viable SARS-CoV-2 after immunosuppressive therapy for cancer. *N Engl J Med*. 2020;**383**(26):2586–8.
15. Bird PW, Badhwar V, Kennedy B, Ladani S, Tang JW. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seroconversion in hematology-oncology patients. *J Med Virol*. 2021;**93**(7):4585–91.

