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Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study

Francesco Passamonti, Chiara Cattaneo, Luca Arcaini, Riccardo Bruna, Michele Cavo, Francesco Merli, Emanuele Angelucci, Mauro Krampera, Roberto Cairoli, Matteo Giovanni Della Porta, Nicola Fracchiolla, Marco Ladetto, Carlo Gambacorti Passerini, Marco Salvini, Monia Marchetti, Roberto Lemoli, Alfredo Molteni, Alessandro Busca, Antonio Cuneo, Alessandra Romano, Nicola Giuliani, Sara Galimberti, Alessandro Corso, Alessandro Morotti, Brunangelo Falini, Atto Billio, Filippo Gherlinzoni, Giuseppe Visani, Maria Chiara Tisi, Agostino Tafuri, Patrizia Tosi, Francesco Lanza, Massimo Massaia, Mauro Turini, Felicetto Ferrara, Carmela Gurreri, Daniele Vallisa, Maurizio Martelli, Enrico Derenzini, Attilio Guarini, Annarita Conconi, Annarosa Cuccaro, Laura Cudillo, Domenico Russo, Fabrizio Ciambelli, Anna Maria Scattolin, Mario Luppi, Carmine Selleri, Elettora Ortu La Barbera, Celestino Ferrandina, Nicola Di Renzo, Attilio Olivieri, Monica Bocchia, Massimo Gentile, Francesco Marchesi, Pellegrino Musto, Augusto Bramante Federici, Anna Candoni, Adriano Venditti, Carmen Fava, Antonio Pinto, Piero Galleni, Luigi Rigacci, Daniele Armiento, Fabrizio Pane, Margherita Oberti, Patrizia Zappasodi, Carlo Visco, Matteo Franchi, Paolo Antonio Grossi, Lorenza Bertù, Giovanni Corraro, Livio Pagano, Paolo Corradini, on behalf of the ITA-HEMA-COV Investigators

Summary

Background Several small studies on patients with COVID-19 and haematological malignancies are available showing a high mortality in this population. The Italian Hematology Alliance on COVID-19 aimed to collect data from adult patients with haematological malignancies who required hospitalisation for COVID-19.

Methods This multicentre, retrospective, cohort study included adult patients (aged ≥18 years) with diagnosis of a WHO-defined haematological malignancy admitted to 66 Italian hospitals between Feb 25 and May 18, 2020, with laboratory-confirmed and symptomatic COVID-19. Data cutoff for this analysis was June 22, 2020. The primary outcome was mortality and evaluation of potential predictive parameters of mortality. We calculated standardised mortality ratios between observed death in the study cohort and expected death by applying stratum-specific mortality rates of the Italian population with COVID-19 and an Italian cohort of 31993 patients with haematological malignancies without COVID-19 (data up to March 1, 2019). Multivariable Cox proportional hazards model was used to identify factors associated with overall survival. This study is registered with ClinicalTrials.gov, NCT04352556, and the prospective part of the study is ongoing.

Findings We enrolled 536 patients with a median follow-up of 20 days (IQR 10–34) at data cutoff, 85 (16%) of whom were managed as outpatients. 440 (98%) of 451 hospitalised patients completed their hospital course (were either discharged alive or died). 198 (37%) of 536 patients died. When compared with the general Italian population with COVID-19, the standardised mortality ratio was 2·04 (95% CI 1·77–2·34) in our whole study cohort and 3·72 (2·86–4·64) in individuals managed as outpatients. 440 (98%) of 451 hospitalised patients completed their hospital course (were either discharged

Interpretation This study adds to the evidence that patients with haematological malignancies have worse outcomes than both the general population with COVID-19 and patients with haematological malignancies without COVID-19. The high mortality among patients with haematological malignancies hospitalised with COVID-19 highlights the need for aggressive infection prevention strategies, at least until effective vaccination or treatment strategies are available.

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Research in context

Evidence before this study
Several small studies are available describing the natural history of patients with haematological malignancies and COVID-19, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We searched PubMed for studies of any type on any haematological malignancy published in English up to July 1, 2020, using the terms “COVID-19” and “haematological malignancy”. The peer-reviewed literature dedicated to patients with SARS-CoV-2 infection and haematological malignancies was mostly limited to case reports or small series. Three small cohorts (the largest with 34 cases), not encompassing the whole spectrum of disease subtypes and treatments, suggested poor outcomes for this patient group, with a case fatality of 32–61%. One paper on chronic lymphocytic leukaemia reported an overall case fatality rate of 33%, but with 25% of patients still in hospital. In this study, so-called watch-and-wait and treated cohorts had similar rates of mortality (37% vs 32%). As a result of the few studies available, statistical analysis is not yet sufficiently robust to assess events and risk factors that can predict death in this new clinical setting.

Added value of this study
To our knowledge, we report the largest series of patients with haematological malignancies and COVID-19 to date.

Our population consists of most haematological malignancies with varying disease status, including patients with a wide age distribution, some of whom were on active treatment. Our findings of high overall mortality (37%) and excess of mortality in patients with haematological malignancies and COVID-19 compared with patients with haematological malignancies without COVID-19, as well as with the Italian population with COVID-19, will assist haematologists and national health commissions in their decision making processes regarding preventive measures and treatment in this patient population.

Implications of all the available evidence
The high mortality in this population of patients, some with the potential to receive curative treatment, has important practical implications for health-care systems: priority must be given to regular swab testing, development of specific treatment trials, and allocation of dedicated health-care resources toward this patient population. Withholding specific effective treatments during the pandemic does not seem to be justified, particularly as the immunosuppressive effect of treatments can be long lasting. If a vaccine becomes available, plans should be established for vaccinations of patients with haematological malignancies, their caregivers, and health-care workers.

Methods

Study design and participants
This multicentre, retrospective, cohort study involved 66 haematology units in Italy (appendix pp 11–12). The ITA-HEMA-COV group worked on behalf of all Italian societies dealing with haematology: Società Italiana di Ematologia, Società Italiana di Ematologia Sperimentale, Gruppo Italiano Trapianto Midollo Osseo, Sorveglianza Epidemiologica Infezioni nelle Emopatie, and Fondazione Italiana Linfomi. We included consecutive adult patients (aged ≥18 years) with any comorbidity who were admitted to hospital in Italy. The trial was approved by the institutional review board of each medical institution. Written informed consent was collected from all patients except for those patients who were unable to give it (according to Italian law 9/2016 Autorizzazione Generale Garante della Privacy).

Verona, Verona, Italy
(C Visco MD; Prof M Krampera MD); Hematology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy (R Caroli MD); Humanitas Clinical and Research Hospital–IRCCS and Department of Biomedical Sciences, Humanitas University, Milan, Italy (M G Della Porta MD); Fondazione IRCCS Ca’ Granda--Ospedale Maggiore Policlinico, Milan, Italy (N Fracchiolla MD); Dipartimento di Medicina e Chirurgia, Università degli Studi di Milano-Bicocca, Milan, Italy; National Centre for Healthcare Research and Pharmacopoeidiology, Milan, Italy (M Franchi, Prof G Corrao); Dipartimento di Medicina interna e Specialità mediche, University of Genoa, Genoa, Italy (Prof B Falini MD); Hematology, ASST Cremona, Cremona, Italy (A Mottieri MD); Stem Cell Transplant Center, AOU Città’ della Salute e della Scienza, Turin, Italy (A Rusca MD); Hematology, Azienda Ospedaliero Universitaria Sant’Anna, Ferrara, Italy (Prof A Cuneo MD); Hematology, Dipartimento di Chirurgia e Specialità Medico-Chirurgiche, Università degli Studi di Catania, Catania, Italy (A Romano MD); Dipartimento di Medicina e Chirurgia, University of Parma, Parma, Italy (N Guelati MD); Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy (S Galbente MD); Hematology, ASST Ovest Milanesi, Milan, Italy (A Cano MD); Department of Clinical and Biological Sciences, Università di Torino, Turin, Italy (A Montorsini MD; C Fava MD); Department of Medicine, University of Perugia, Perugia, Italy (Prof B Falini MD); Ospedale di Bolzano, Bolzano, Italy (A Billo MD); Hematology, worldwide, with comorbidities shown to affect disease severity and patient outcomes. 7–14 Severe cases of COVID-19 are characterised by an intense immune response with subsequent cytokines release syndrome and endothelial damage. 7 Among patients with COVID-19, 3–7% have been found to have conditions characterised by immunodeficiency. 8 The potential threat of COVID-19 to patients who are immunocompromised because of cancer is thought to be substantial. 9–13

Haematological malignancies such as leukaemias, myelodysplastic syndromes, myeloproliferative neoplasms, lymphomas, and multiple myeloma can be potentially cured or have an improved survival in a sizeable fraction of cases; therefore, infections can shorten life expectancy. Patients with haematological malignancies usually have long-lasting immunodeficiency because of the malignancy itself, anticancer treatments, or as a consequence of procedures such as haematopoietic stem-cell transplantation. Several small studies including case reports 15–18 and small retrospective cohort studies 19–20 have been published on the outcome of patients with haematological malignancies and COVID-19. As of June 22, 2020 (data cutoff for our study), Italy had 239 627 cases of COVID-19 according to the Istituto Superiore di Sanità, of whom 33 498 (13·9%) died. The aim of the Italian Hematology Alliance on COVID-19 (ITA-HEMA-COV) project was to collect and analyse data from adult patients with haematological malignancies who required hospitalisation for COVID-19. Here, we report results from a cohort study of 66 hospitals in Italy. This effort will assist haematologists worldwide and National Health Commissions in their decision making process regarding preventive measures and treatment in this patient population.
Procedures
Data on laboratory parameters, possible complications, drug exposure, and patient outcomes (ie, intensive care unit [ICU] admission, death, or hospital discharge) were collected for all patients during hospitalisation. Data on patient characteristics and outcomes were extracted by study investigators from electronic medical records or clinical charts, including age, sex, Charlson Comorbidity Index, type and status of haematological malignancy, time since diagnosis of haematological malignancy to COVID-19 diagnosis, time from last haematological malignancy therapy to COVID-19 diagnosis, and COVID-19 severity.

Diagnosis of haematological malignancy was made on the basis of the most recent WHO classification of haematopoietic tumours.20,21 We defined a patient as having progressive disease when the malignancy was not responding to active therapy and remission as no evidence of disease. We defined active therapy as a therapy delivered during admission for COVID-19 or that had ended within the past 3 months. All nasopharyngeal swabs for COVID-19 diagnosis were managed according to national recommendations.22 Severity of COVID-19 at admission was graded according to the China Centers for Disease Control and Prevention definitions: mild (non-dyspnoea, respiratory failure, septic shock, or multiple organ dysfunction or failure).2

Mortality estimates for COVID-19 in the general Italian population were obtained from the Bollettino Sovrigenza Integrato of the Istituto Superiore di Sanità, released on June 23, 2020.23 Mortality for patients with haematological malignancies without COVID-19 was calculated using data from 31 993 patients resident in Lombardy, who were diagnosed with haematological malignancies from Jan 1, 2007, to Feb 29, 2019, and were still alive on March 1, 2019 (non-COVID-19 cohort).

Outcomes
The primary outcomes were mortality among patients with haematological malignancies and COVID-19 and evaluation of potential predictive parameters of mortality, including biochemical parameters (haemoglobin, haematocrit, platelets, leucocytes, lymphocytes, clotting tests, serum lactate dehydrogenase, and C-reactive protein), haematological malignancy characteristics (disease type, disease status, and therapy status), and COVID-19 severity. Secondary outcomes were epidemiology of patients with haematological malignancies infected by SARS-CoV-2 (ie, type of haematological malignancy, ICU admission rate, laboratory abnormalities, and haematological malignancy-specific treatments), evolution of haematological malignancies, and dynamics of viral load; results for the latter two are not presented in this Article. Although the presupposed plan was to report on the epidemiological outcomes at 6 months of follow-up, we report these outcomes early because the majority of patients had completed their hospital stay.

Statistical analysis
Continuous variables are expressed as mean (SD) or median (IQR). We used the independent group t test to analyse normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed continuous variables. Normality was verified using the Shapiro-Wilk test and graphically using Q–Q plot. Categorical variables are presented as frequencies and percentages, and were analysed using the χ² test. Characteristics of the study population were described for survivors and non-survivors and overall incidence of ICU admission was calculated. Among patients with severe or critical COVID-19, the Fine and Gray model was applied to study patient characteristics (age, Charlson Comorbidity Index, type and status of haematological malignancy) associated with ICU admission, treating death as a competing event in the univariate model. The features of our cohort study were finally compared according to COVID-19 severity (severe or critical vs mild) using the t test, Mann-Whitney U test, or χ² test, as appropriate.

The mortality rate for COVID-19 was calculated as the ratio between the number of deaths in patients with COVID-19 and the person-time at risk. Person-time was calculated as the time between date of COVID-19 diagnosis and date of death by any cause, hospital discharge, or last follow-up, whichever occurred first. In a post-hoc analysis, Poisson regression models were used to compare mortality of patients enrolled in the first period of the study (Feb 25–March 31) versus those enrolled in the second period (April 1–May 18) and between individuals treated in northern versus southern Italy (including Sardinia and Sicily). We compared overall survival in patients with different COVID-19 severity by Kaplan-Meier with the log rank test. We provide two standardised mortality ratios: one comparing mortality of the study cohort with that of the general Italian population with COVID-19 and the second comparing mortality of the study cohort with the Lombardy population with haematological malignancies without COVID-19 (non-COVID-19 cohort). Standardised mortality ratios are calculated as the ratio between observed deaths in the study cohort and expected deaths, calculated as stratum-specific mortality rates of the comparison cohorts (indirect standardisation). When comparing with the general Italian population with COVID-19, mortality rates were stratified according to sex and age. When comparing with the non-COVID-19 cohort, mortality rates in the comparison cohort were calculated in the period March 1–June 22, 2019 (ie, the equivalent time period of the study cohort, but in 2019) and were stratified according to sex, age, type of haematological malignancy, and disease duration. Wald 95% CIs were calculated by assuming observed deaths followed a Poisson
536 patients with haematological malignancies who were admitted for inpatient (n=451) or outpatient (n=85) care to manage symptomatic COVID-19 were enrolled (figure 1). Median follow-up was 20 days (IQR 10–34; range 1–98), with last contact on June 22. Among 451 hospitalised patients, 440 (98%) completed their hospital course (were either discharged or died) with a median length of hospital stay of 16 days (9–29; range 1–98); median length of hospital stay was 20 days (12–36; range 2–98) for survivors and 11 days (6–21; range 1–78) for non-survivors. 82 (18%) of 451 hospitalised patients required ICU admission: 50 (11%) patients required immediate admission to the ICU whereas 32 (8%) of 401 patients who were initially not admitted to the ICU were later transferred there. Within patients with severe or critical COVID-19—ie, potential candidates for ICU admission—the Fine and Gray model showed that those admitted to the ICU were younger (hazard ratio [HR] 0·97, 95% CI 0·90–0·98) and had a lower Charlson Comorbidity Index (HR 0·80, 0·71–0·91).

Patients’ baseline characteristics are shown in table 1 by survival status, with haematological malignancies subtypes detailed in the appendix (pp 2–3). The most common symptoms at time of hospital admission for COVID-19 were fever (337 [75%] of 451 patients), dyspnoea (231 [51%] patients), cough (204 [45%] patients), and malaise (175 [39%] patients; appendix p 4). Vascular events were evident in 33 (5%) patients (appendix p 4). Headaches occurred in 28 (6%) patients and diarrhoea in 42 (9%) patients.

268 (50%) of 536 patients had mild COVID-19 (84 of whom were managed as outpatients), 194 (36%) patients had severe COVID-19 (one of whom was managed as an outpatient), and 74 (14%) patients had critical COVID-19 (figure 1). Clinical characteristics by COVID-19 severity are reported in the appendix (p 5). In univariate analysis, patients with severe or critical disease were older (mean age 68·0 years [SD 13·7] vs 65·5 years [13·7]; p=0·032), had a higher Charlson Comorbidity Index (mean 5·0 [2·3] vs 4·4 [2·4]; p=0·011), and a more recent diagnosis of haematological malignancy (median time from diagnosis 0 years [IQR 2–6] vs 1 year [0–5]; p=0·0032) than patients with mild COVID-19 (appendix p 5).

At data cutoff, 198 (37%) of 536 patients had died, with a mortality rate of 153·2 deaths (95% CI 129·7–172·1) per 10 000 person-days. During the first study period (Feb 25–March 31), the mortality rate was 169·2 deaths (95% CI 143·9–198·9) per 10 000 person-days, whereas during the second study period (April 1–May 18) it was significantly lower, at 111·1 deaths (84·4–146·2) per 10 000 person-days (Wald $\chi^2$ test; p=0·014). No significant difference in mortality rate was detected between northern (150·8 deaths [129·4–175·9] per 10 000 person-days) and southern (141·6 deaths [101·7–197·2] per 10 000 person days) Italy (Wald $\chi^2$ test; p=0·73). 52 (63%) of 82 patients admitted to the ICU and 146 (32%) of 451 admitted to the ICU were younger (hazard ratio [HR] 0·97, 95% CI 0·90–0·98) and had a lower Charlson Comorbidity Index (HR 0·80, 0·71–0·91).
454 patients not admitted to the ICU died. Patients with severe or critical COVID-19 had worse overall survival than patients with mild COVID-19 (appendix p 10).

When comparing mortality in the study cohort with the Italian population with COVID-19, the standardised mortality ratio was 2.04 (95% CI 1.77–2.34) in the whole study population, 3.72 (2.86–4.64) in people younger than 70 years, and 1.71 (1.44–2.04) in people aged 70 years or older (figure 2). When comparing mortality in the study cohort with the non-COVID-19 cohort with haematological malignancies, 853 (2.7%) of 31935 patients in the non-COVID-19 cohort died, with a mortality rate of 2.42 deaths (2.26–2.58) per 10,000 person-days and a resulting standardised mortality ratio of 41.3 (38.1–44.9).

In the multivariable Cox regression model, older age; progressive disease status; diagnosis of acute myeloid leukaemia, indolent non-Hodgkin lymphoma, aggressive non-Hodgkin lymphoma, or plasma cell neoplasms; and severe or critical COVID-19 at admission were associated with worse survival (table 2).

In an exploratory analysis in 308 patients with data on laboratory findings at admission (176 survivors, 132 non-survivors), non-survivors had lower haemoglobin values (median difference –1.5 g/dL, 95% CI –2.0 to –0.2) and platelet count (−65 000 platelets per μL, –95 250 to –17 000) and higher serum lactate dehydrogenase (125 U/L, 56 to 215) than did survivors (appendix p 6).

251 (56%) of 451 patients had at least one complication during hospitalisation. Additional infections occurred in 187 (41%) of 451 patients, alteration of organ damage biomarkers in 124 (27%) patients, and vascular events in 50 (11%) patients. The proportion of non-survivors experiencing complications was numerically higher than the proportion of survivors (figure 3). After admission, treatments for COVID-19 were administered according to institutional guidelines (appendix p 7). In the 451 hospitalised patients, 295 (65%) patients were treated with hydroxychloroquine (of whom 99 [34%] died), 188 (42%) with antiviral agents (of whom 71 [38%] died), and 40 (9%) with tocilizumab (of whom 16 [40%] died).

82 patients underwent haematopoietic stem-cell transplantation before SARS-CoV-2 infection, 31 (38%) of which were allogeneic (appendix p 8). Death occurred in 11 (35%) of 31 patients who received allogeneic haematopoietic stem-cell transplantation and in 17 (33%) of 51 who received autologous transplantation. 16 allogeneic transplantations and three autologous transplantations had been done in the previous 6 months; four of these patients died, all of whom had received allogeneic transplantation.

233 patients were on active therapy when diagnosed with COVID-19, 90 (39%) of whom died (appendix p 9). Of patients with acute myeloid leukaemia, 11 (33%) of 33 patients receiving chemotherapy and one (12%) of eight patients on azacytidine–decitabine died. Among patients with myeloproliferative neoplasms, all 11 patients with chronic myeloid leukaemia receiving tyrosine kinase inhibitors (TKIs) were alive at data cutoff, whereas four (44%) of nine patients with polycythaemia vera or
myelofibrosis receiving ruxolitinib died. Among patients with non-Hodgkin lymphomas, four (31%) of 13 patients on rituximab alone as maintenance, 27 (47%) of 57 on rituximab-chemotherapy, and eight (44%) of 18 on chemotherapy alone died. Nine patients with chronic lymphocytic leukaemia were receiving ibrutinib at the time of COVID-19 diagnosis, of whom five (56%) died. Immunomodulatory drugs were given to 19 patients with non-Hodgkin lymphomas, four (31%) of 13 patients with chronic lymphocytic leukaemia, and one (14%) of seven patients with acute myeloid leukaemia. Immunosuppressive therapies were given to 20 patients with chronic lymphocytic leukaemia, four (31%) of 13 patients with non-Hodgkin lymphomas, and one (14%) of seven patients with acute myeloid leukaemia.

### Discussion

In the COVID-19 pandemic, patients with haematological malignancies are potential high-risk populations because of intrinsic frailty, immunosuppressive therapies, and frequent hospital visits for treatment delivery. In our study, 198 (37%) of 536 patients with haematological malignancies died by data cutoff. Some smaller cohorts have found similarly poor outcomes for this patient group, with mortality ranging from 32% to 61% of cohorts have found similarly poor outcomes for this patient group, with mortality ranging from 32% to 61% of patients.17,18

Clinical features of COVID-19 reported from the Chinese population were mainly fever (44% on admission) and cough (68%), with 5% of patients admitted to the ICU.19 Mortality was 1.4% in a Chinese study including 926 patients with non-severe COVID-19,20 rising when patients with severe disease were included: mortality was 10% in 393 cases from two centres in the New York City area (with 33% of patients receiving invasive mechanical ventilation)21 and 21% in 5700 cases from the Northwell COVID-19 Research Consortium (14% of whom were admitted to the ICU).22 In patients who received a solid organ transplantation, the mortality rate has been found to be around 20–30%.23,24

Our study population developed COVID-19-related symptoms similarly to those reported in healthy individuals, which suggests a common host response to the virus. However, severe forms of disease were more frequent in patients with haematological malignancies: dyspnoea occurred in 51% of patients (vs 17–3% in New York City3 and 19% in China6) and fever in 75% of patients (vs 7–15%).11,13

#### Table 2: Independent predictors of mortality from multivariable Cox regression model

| Type of haematological malignancy | Deaths/patients Hazard ratio (95% CI) |
|----------------------------------|---------------------------------------|
| Acute myeloid leukaemias         | 48/81 2·10 (1·41–3·12)                |
| Myelodysplastic syndromes        | 22/69 1·64 (0·77–3·51)                |
| Myelofibrosis                    | 22/69 1·64 (0·77–3·51)                |
| Acute lymphoblastic leukaemias   | 3/16 1·65 (0·46–5·94)                 |
| Hodgkin lymphomas                | 3/17 1·30 (0·36–4·66)                 |
| Indolent lymphomas               | 21/54 2·19 (1·07–4·48)                |
| Plasma cell neoplasms            | 39/106 2·48 (1·31–4·69)               |
| Aggressive lymphomas             | 41/99 2·56 (1·34–4·89)                |
| Chronic lymphoproliferative neoplasms | 22/69 1·64 (0·77–3·51) |
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| Plasma cell neoplasms            | 39/106 2·48 (1·31–4·69)               |
| Aggressive lymphomas             | 41/99 2·56 (1·34–4·89)                |
| Chronic lymphoproliferative neoplasms | 22/69 1·64 (0·77–3·51) |

Per point increase

Deaths/patients Hazard ratio

| Type of haematological malignancy | Deaths/patients Hazard ratio (95% CI) |
|----------------------------------|---------------------------------------|
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| Plasma cell neoplasms            | 39/106 2·48 (1·31–4·69)               |
| Aggressive lymphomas             | 41/99 2·56 (1·34–4·89)                |

Within patients with severe or critical COVID-19, this finding clearly indicates that patients with haematological malignancies represent a high-risk population. Overall, 50% of our patients had severe or critical COVID-19. This finding clearly indicates that patients with haematological malignancies represent a high-risk population. Mild symptoms such as headache and diarrhoea occurred in less than 10% of our patients, which suggests a common host response to the virus. However, severe forms of disease were more frequent in patients with haematological malignancies: dyspnoea occurred in 51% of patients (vs 17–3% in New York City3 and 19% in China6 and fever in 75% of patients (vs 31% in New York City). Mild symptoms such as headache and diarrhoea occurred in less than 10% of our hospitalised patients, similarly to the general population.14 Overall, 50% of our patients had severe or critical COVID-19. This finding clearly indicates that patients with haematological malignancies represent a high-risk population with poor COVID-19 outcomes, even when compared with patients with solid tumours (17% rate of case fatality). This is also evident by the high proportion (18%) of patients admitted to the ICU, which is similar to that reported in patients with solid tumours (7–15%).23,24 Insufficient ICU capacity is one of the known problems of the COVID-19 pandemic, since those with severe disease who are excluded have reduced chance of survival. Within patients with severe or critical disease, we found that those admitted to the ICU were younger and had a lower Charlson Comorbidity Index than those who were not admitted. Measures to reduce outbreak magnitude in this pandemic, such as preventive measures, would be needed to reduce the proportion of patients admitted to the ICU.
lockdowns and physical distancing measures, are imperative to ensure less pressure on ICUs.

When comparing mortality in our cohort with the general population with COVID-19, the standardised mortality ratio in patients younger than 70 years was 3.72, meaning that mortality of patients with haematological malignancies and COVID-19 was nearly four times higher than that of the general population with COVID-19. In the haematology setting, patients younger than 70 years are often candidates for treatments such as haematopoietic stem-cell transplantation and they have a high chance of achieving potential cure or long-term survival. When comparing our cohort with a non-COVID-19 cohort with haematological malignancies, we found a standardised mortality ratio of 41.3, meaning that mortality of patients with haematological malignancies and COVID-19 was 41 times higher than that of such patients without SARS-CoV-2 infection. We found a mortality rate of 2.42 deaths per 10,000 person-days in patients with haematological malignancies in 2019, which increased to 153.2 deaths per 10,000 person-days in patients with COVID-19 who were managed in 2020. This information has important practical implications for health-care systems: priority should be given to regular swab testing, development of specific treatment trials, and allocation of dedicated health-care resources towards this category of patients.

Overall survival was independently predicted by age, type of malignancy, disease status, and the severity of COVID-19. We found that older age was significantly associated with worse overall survival, as expected from data in the general population, whereas comorbidities were not. In addition, progressive disease status and diagnosis of acute myeloid leukaemia, non-Hodgkin lymphomas, and plasma cell neoplasms were predictive for a poor outcome. Progressive disease status is also associated with COVID-19 survival in solid cancer cohorts.31 We found no association between overall survival and time since haematological malignancy diagnosis or last treatment for haematological malignancies. Thus, it seems that patients with haematological malignancies are at high risk of mortality regardless of whether they have recent disease or are on specific therapy, or both. Finally, our data showed that COVID-19 severity was independently associated with worse overall survival.

A study on solid cancers has shown that cytotoxic chemotherapy delivered within 4 weeks before COVID-19 diagnosis had no effect on overall survival.14 We therefore investigated COVID-19 mortality according to treatment in the 233 patients who were receiving therapy at the time of COVID-19 diagnosis or who had received therapy within the previous 3 months (immunosuppressive effect of treatments is mostly long lasting). Of note, all patients with chronic myeloid leukaemia who received TKIs were still alive at data cutoff, suggesting these patients, when receiving optimal care, have a well controlled disease and are thus at low risk of mortality according to the predictors we identified. We also found lower mortality in patients with follicular lymphoma receiving rituximab as maintenance therapy after remission (31%) than when combined with chemotherapy (47%), which was similar to mortality in patients treated with chemotherapy alone (44%).

When taken together, our findings suggest that withholding specific effective treatments from patients with haematological malignancies during the COVID-19 pandemic is not justified, especially as the immunosuppressive effect of treatments is long lasting. In the case of SARS-CoV-2 infection, disease type and status are the major drivers of outcome.

The data we present on mortality might facilitate patient–doctor communication on COVID-19-related risks for patients with haematological malignancies. We conclude that meticulous preventive measures are crucial in this setting and future trials on specific antiviral treatments are urgently required. If a COVID-19 vaccine is successfully developed, plans must be established for future priority vaccination of patients, caregivers, and health-care workers.

Data from randomised controlled trials on COVID-19 treatments have not shown any benefit for remdesivir,34 lopinavir–ritonavir,27 or hydroxychloroquine.39 Preliminary data have shown that tocilizumab, a monoclonal antibody targeting interleukin-6 receptor, can improve the clinical outcome in patients with severe or critical disease.27 Our study adds some preliminary information on drugs that are currently under investigation for treatment of COVID-19, such as ruxolitinib, a Janus kinase inhibitor,16 and ibrutinib, a Bruton TKI. We found that 44% of patients receiving ruxolitinib and 55% of patients receiving ibrutinib died. Our data did not indicate a clear protective or adverse effect of Bruton TKI therapy, as reported by Mato and colleagues.45

Limitations of our study include the retrospective nature of the study, the lack of power to support firm conclusions, the heterogeneity of haematological malignancies
included, and potential issues with generalisability to non-haematological malignancies, benign haematological disorders, or cancer. We did not include patients who were asymptomatic or were not tested for SARS-CoV-2 infection (during February and March, routine swab testing of asymptomatic people was not allowed by the Italian Government), which is likely to have resulted in a higher mortality rate in our cohort.

In conclusion, the high mortality among patients with haematological malignancies who were hospitalised with COVID-19 highlights the need for aggressive infection prevention, at least until effective vaccination or treatment strategies are available. Delivering efficient therapies for haematological malignancies despite the pandemic continues to be a challenge needing further research.

**Contributors**
FrP served as the principal investigator. FrP and PC contributed to study design, study supervision, and data interpretation and wrote the paper. FrP, PC, LP, CC, LA, FMe, CV, RC, MGDP, MS, PM, and PAG conceived the study. LB, MF, and GC did the statistical plan and interpreted the data. MS did the literature search and interpreted data. FrP, CC, LA, RB, MC, FMe, EA, MK, RC, MGDP, NF, MLA, CGP, MS, MoM, RL, AMol, Al, ABi, ABu, ACan, AR, NG, SG, AC, AMor, BF, ABI, FG, GV, MCT, AT, FT, FL, MaxM, MT, FF, CG, LP, DV, MaxM, ED, AG, ACo, ACo, LC, DR, FC, AMS, Mlu, CS, EOLB, Cfe, NDR, AO, MB, MG, FMA, PM, ABF, ACA, AV, Cfa, AP, PG, LR, DA, FAP, MO, and PZ recruited participants and collected and interpreted data. All authors contributed to manuscript writing and review of the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Declaration of interests**
We declare no competing interests.

**Data sharing**
Individual participant data that underlie the results reported in this Article, after de-identification (text, tables, figures, and appendices), will be available together with the study protocol. This will be from 9 to 24 months following Article publication. Data will be available only for investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. Proposals should be directed to lorena.berto@uninovubria.it; to gain access, data requestors will need to provide a draft of a data access agreement that will be evaluated.

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**References**
1 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–506.
2 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; published online Feb 24. https://doi.org/10.1001/jama.2020.2648.
3 Richardson S, Hirsch IS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020; 323: 2052–59.
4 Gowda P, Chui JJ, Finheiro LC, et al. Clinical characteristics of COVID-19 in New York City. N Engl J Med 2020; 382: 2372–74.
5 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054–62.
6 Guan WJ, Liang W, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020; 55: 2000547.
7 Moore BJ, June CH. Cytokine release syndrome in severe COVID-19. Science 2020; 368: 673–74.
8 CDC COVID-19 Response Team. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019—United States, February 12–March 28, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 382–86.
9 Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020; 21: 335–37.
10 Kudener NM, Ghoseiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet 2020; 395: 1917–18.
11 Lee LYW, Cazier JB, Starkey T, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet 2020; 395: 1919–26.
12 Tian J, Yuan X, Xiao J, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol 2020; 21: 904–13.
13 Yang K, Sheng Y, Huang C, et al. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. Lancet Oncol 2020; 21: 904–13.
14 Zhang X, Song K, Tong F, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. Blood Adv 2020; 4: 1307–10.
15 Jin XH, Zheng KL, Pan KH, Xie YP, Zheng MH. COVID-19 in a patient with chronic lymphocytic leukaemia. Lancet Haematol 2020; 7: e351–52.
16 Huang J, Lin H, Wu Y, et al. COVID-19 in posttransplant patients—report of 2 cases. Am J Transplant 2020; 20: 1879–81.
17 He W, Chen L, Yuan G, et al. COVID-19 in persons with haematological malignancies. Leukemia 2020; 34: 1637–45.
18 Martin-Moro F, Marquet J, Piris M, et al. Survival study of hospitalized patients with concurrent Covid-19 and haematological malignancies. Br J Haematol 2020; 190: e16–20.
19 Malard F, Genthon A, Brissot E, et al. COVID-19 outcomes in patients with hematologic disease. Bone Marrow Transplant 2020; 6: 1–5.
20 Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016; 127: 2391–405.
21 Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016; 127: 2375–90.
22 Istituto Superiore di Sanità. Rapporto ISS COVID-19 n. 11/2020 Rev. 2. Raccomandazioni per il corretto prelievo, conservazione e analisi sul tampone oro/rino-faringeo per la diagnosi di COVID-19. May 29, 2020. https://www.iss.it/rapporti-covid-19/-/asset_publisher/fw1826wzyl/content/id/5129985 (accessed Aug 4, 2020).
23 Istituto Superiore di Sanità. Sorveglianza Integrata COVID-19 in Italia. June 22, 2020. https://www.epicentro.iss.it/coronavirus/bollettino/Infografica_22giugno%20ITA.pdf (accessed July 28, 2020).
24 Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter. Am J Transplant 2020; 20: 1800–08.
25 Latif F, Farr MA, Clerkin KJ, et al. Characteristics and outcomes of recipients of heart transplant with coronavirus disease 2019. JAMA Cardiol 2020; 5: e200159.
26 Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020; 395: 1569–78.
27 Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020; 382: 1787–99.
28 Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020; 382: 2411–18.

29 Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci USA 2020; 117: 10970–75.

30 Passamonti F, Maffioli M. The role of JAK2 inhibitors in MPNs 7 years after approval. Blood 2018; 131: 2426–35.

31 Mato AR, Roeker LE, Lamanna N, et al. Outcomes of COVID-19 in patients with CLL: a multicenter, international experience. Blood 2020; published online July 20. https://doi.org/10.1182/blood.2020006965.