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 Turrini, Felicetto Ferrara, Carmela Gurrieri, 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, Elettra 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 Galieni, Luigi Rigacci, Daniele Armiento, Fabrizio Pane, Margherita Oberti, Patrizia Zappasodi, Carlo Visco, Matteo Franchi, Paolo Antonio Grossi, Lorenza Bertù, Giovanni Corrao, 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 31 993 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 younger than 70 years. When compared with the non-COVID-19 cohort with haematological malignancies, the standardised mortality ratio was 41·3 (38·1–44·9). Older age (hazard ratio 1·03, 95% CI 1·01–1·05); progressive disease status (2·10, 1·41–3·12); diagnosis of acute myeloid leukaemia (3·49, 1·56–7·81), indolent non-Hodgin lymphoma (2·19, 1·07–4·48), aggressive non-Hodgkin lymphoma (2·56, 1·34–4·89), or plasma cell neoplasms (2·48, 1·31–4·69), and severe or critical COVID-19 (4·08, 2·73–6·09) were associated with worse overall survival.

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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Department of Medicine and Surgery, University of Insubria and ASST Sette Laghi, Ospedale di Circolo of Varese, Varese, Italy (Prof F Passamonti MD, M Salvini MD, Prof P A Grossi MD, L Bertù, PhD); **Haematology, ASST-Spedali Civili, Brescia, Italy** (C Cattaneo MD, M Oberti MD); **Department of Molecular Medicine, University of Pavia, Pavia, Italy** (Prof L Arcaini MD); **Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy** (Prof L Arcaini, P Zappasodi MD); **Division of Hematology, Department of Translational Medicine, University of Eastern Piedmont and Ospedale Maggiore della Carità, Novara, Italy** (R Bruna MD); **Seràgnoli Institute of Hematology, Department of Experimental, Diagnostic and Specialty Medicine, Bologna University School of Medicine, Bologna, Italy** (Prof M Cavo MD); **Hematology, Azienda USL-IRCCS Reggio Emilia, Reggio Emilia, Italy** (F Merli MD); **Hematology, Ospedale Policlinico San Martino, Genoa, Italy** (E Angelucci MD); **Department of Medicine, Section of Hematology, University of**

Introduction

An outbreak of a previously unknown coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first detected in Wuhan, China, in December, 2019.[1] In March, 2020, WHO declared COVID-19, the disease caused by SARS-CoV-2, a global pandemic. As of Aug 2, 2020, there have been more than 18·1 million cases of SARS-CoV-2 infection

Verona, Verona, Italy (C Visco MD, Prof M Krampera MD); Hematology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy (R Cairoli 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); Hematology, Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy (M Marchetti MD, M Ladetto MD); Department of Hematology (Prof C Gambacorti Passerini MD) and Laboratory of Healthcare Research & Pharmacoepidemiology, Department of Statistics and Quantitative Methods (M Franchi PhD, Prof G Corrao PhD), Università degli Studi di Milano-Bicocca, Milan, Italy; National Centre for Healthcare Research and Pharmacoepidemiology, Milan, Italy (M Franchi, Prof G Corrao); Dipartimento di Medicina interna e Specialità mediche, University of Genoa, Genoa, Italy (Prof R Lemoli MD); Hematology, ASST Cremona, Cremona, Italy (A Molteni MD); Stem Cell Transplant Center, AOU Citta' della Salute e della Scienza, Turin, Italy (A Busca 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 Giuliani MD); Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy (S Galimberti MD); Hematology, ASST Ovest Milanese, Milan, Italy (A Corso MD); Department of Clinical and Biological Sciences, Università di Torino, Turin, Italy (A Morotti MD, C Fava MD); Department of Medicine, University of Perugia, Perugia, Italy (Prof B Falini MD); Ospedale di Bolzano, Bolzano, Italy (A Billio MD); Hematology,

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.

worldwide, with comorbidities shown to affect disease severity and patient outcomes.[2–6] 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 have usually 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[14–17] and small retrospective cohort studies[17–19] 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.

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 between Feb 25 and May 18, 2020, with data cutoff for the analyses on June 22, 2020. Inclusion criteria were the presence of a WHO-defined haematological malignancy and symptomatic and laboratory-confirmed SARS-CoV-2 infection, tested by RT-PCR on nasopharyngeal swabs. The trial was approved by the institutional review board of each haematology unit. 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).

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-pneumonia and mild pneumonia), severe (dyspnoea, respiratory frequency ≥30 breaths per min, SpO_2 ≤93%, PaO_2/FiO_2 <300, or lung infiltrates >50%), and critical (respiratory failure, septic shock, or multiple organ disfunction or failure).[2]

Mortality estimates for COVID-19 in the general Italian population were obtained from the Bollettino Sorveglianza Integrato of the Isituto 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 prespecified 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-Wilks test and graphically using Q–Q plot. Categorical variables are presented as frequencies and percentages, and were analysed using the χ^2 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 χ^2 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

Ospedale Ca' Foncello, Treviso, Italy (F Gherlinzoni MD); **Dipartimento di Onco-Ematologia, Azienda Ospedaliera Ospedali Riuniti Marche Nord, Pesaro, Italy** (G Visani MD); **Hematology, Ospedale San Bortolo, Vicenza, Italy** (M C Tisi MD); **Hematology, University Hospital Sant'Andrea, Sapienza, Rome, Italy** (Prof A Tafuri MD); **Department of Clinical and Molecular Medicine** (Prof A Tafuri) **and Hematology, Department of Translational and Precision Medicine** (M Martelli MD), **Sapienza, University of Rome, Rome, Italy; Hematology, Ospedale degli Infermi di Rimini, Rimini, Italy** (P Tosi MD); **Hematology, Santa Maria delle Croci, Ravenna, Italy** (F Lanza MD); **Hematology, Santa Croce Hospital, Cuneo, Italy** (M Massaia MD); **Hematology, Ospedale Valduce, Como, Italy** (M Turrini MD); **Hematology, Ospedale Antonio Cardarelli, Naples, Italy** (F Ferrara MD); **Dipartimento Strutturale Aziendale Medicina, University of Padova, Padova, Italy** (C Gurrieri MD); **Hematology, Ospedale di Piacenza, Piacenza, Italy** (D Vallisa MD); **Hematology, Istituto Europeo di Oncologia, Milan, Italy** (E Derenzini MD); **Hematology, Istituto Tumori Giovanni Paolo II, Bari, Italy** (A Guarini MD); **Hematology, Ospedale degli Infermi, Biella, Italy** (A Conconi MD); **Ematologia, USL 6 Livorno, Livorno, Italy** (A Cuccaro MD); **Hematology, San Giovanni Addolorata Hospital, Rome, Italy** (L Cudillo MD); **Dipartimento di Scienze Cliniche e Sperimentali, University of Brescia, Brescia, Italy** (Prof D Russo MD); **Dipartimento Oncologico, ASST Valle Olona, Busto Arsizio, Italy** (F Ciambelli MD); **Hematology, Ospedale dell'Angelo di Mestre, Venice, Italy** (A M Scattolin MD); **Dipartimento di Scienze Mediche e Chirurgiche Materno-Infantili e dell'Adulto, University of Modena and Reggio Emilia, Azienda Ospedaliera Universitaria, Modena, Italy** (Prof M Luppi MD); **Hematology, Ospedale San Giovanni di Dio e Ruggi D'Aragona, Salerno, Italy**

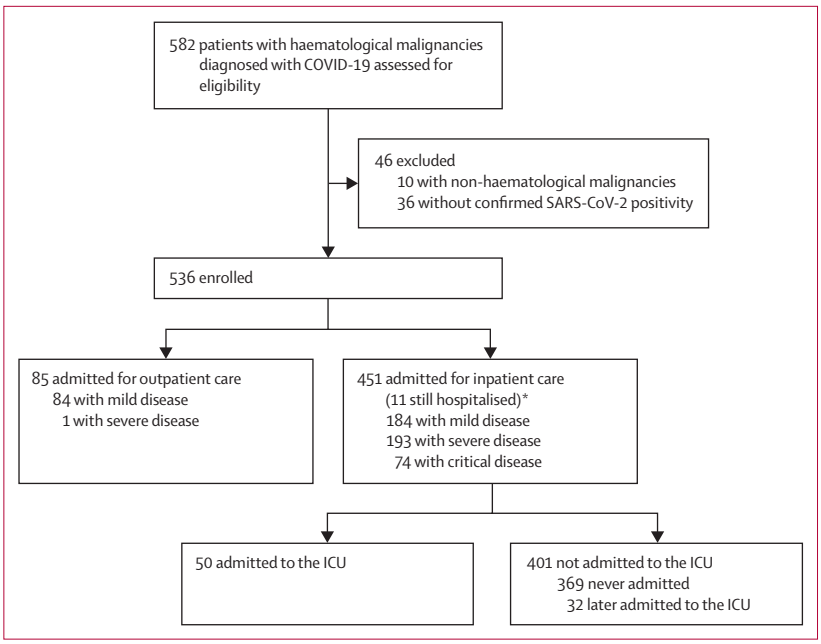

Figure 1: **Study profile**
All patients were included in mortality analyses. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ICU=intensive care unit. *Analysed for complications.

(C Selleri MD); **UOC Ematologia con Trapianto, Ospedale Santa Maria Goretti, Latina, Italy** (E Ortu La Barbera); **Hematology, Ospedale Santa Maria Goretti, Latina, Italy** (E Ortu La Barbera MD); **Hematology, Ospedali Riuniti Azienda Ospedaliera Universitaria di Foggia, Foggia, Italy** (C Ferrandina MD); **Hematology and Transplant Unit, Ospedale Vito Fazzi, Lecce, Italy** (N Di Renzo MD); **Hematology, Ospedali Riuniti di Ancona, Ancona, Italy** (Prof A Olivieri MD); **Hematology Unit, University of Siena, Azienda Ospedaliero Universitaria Senese, Siena, Italy** (M Bocchia MD); **Hematology, Ospedale SS Annunziata, Taranto, Italy** (M Gentile MD); **Hematology and Stem Cell Transplant Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy** (F Marchesi MD); **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** (Prof P Musto MD); **Hematology and Transfusion Medicine, L Sacco University Hospital, Milan, Italy**

distribution. Using a multivariable Cox proportional hazards model, we evaluated association with overall survival of the following variables: age, sex, Charlson Comorbidity Index, type and status of haematological malignancy, time from haematological malignancy to COVID-19 diagnosis, time from last haematological malignancy therapy to COVID-19 diagnosis, and COVID-19 severity. The proportional hazard assumption was tested with incorporation of time-dependent covariates. Multicollinearity was investigated with the variance inflation factor and tolerance. We did an exploratory analysis on the association of biochemical variables with overall survival. For baseline laboratory values, median and 95% CIs were obtained with 1000 bootstrap simulations for survivors and non-survivors separately; the 95% CI for difference of medians between the two groups was also calculated with the same method. Finally, we did a descriptive exploratory analysis on special clinical situations (eg, haematopoietics stem-cell transplantation) and treatments received for haematological malignancies. All statistical analysis was done with SAS version 9.4. This study is registered with ClinicalTrials.gov, NCT04352556, and the prospective part of the study is ongoing.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data and had final responsibility for the decision to submit for publication.

Results

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 0·96–0·98) 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 12·8] *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 (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 χ^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 χ^2 test; p=0·73). 52 (63%) of 82 patients admitted to the ICU and 146 (32%) of

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 31993 patients in the non-COVID-19 cohort died, with a mortality rate of 2·42 deaths (2·26–2·58) per 10000 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 (–65000 platelets per µL, –95250 to –17000) 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), 135 (30%) with heparins (of whom 46 [34%] 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

	All patients (n=536)	Survivors (n=338)	Non-survivors (n=198)
Age, years			
Mean	66·8 (13·3)	64·0 (13·6)	71·5 (11·5)
Median	68 (58–77)	64 (55–73)	73 (66–80)
Age group, years			
<50	62 (12%)	51 (15%)	11 (6%)
50–59	86 (16%)	68 (20%)	18 (9%)
60–69	137 (26%)	100 (30%)	37 (19%)
70–79	158 (29%)	79 (23%)	79 (40%)
≥80	93 (17%)	40 (12%)	53 (27%)
Sex			
Female	196 (37%)	133 (39%)	63 (32%)
Male	340 (63%)	205 (61%)	135 (68%)
Charlson Comorbidity Index			
Mean	4·7 (2·4)	4·2 (2·3)	5·5 (2·3)
Median	4 (3–6)	4 (3–6)	5 (4–7)
Coexisting conditions			
Heart disease	82 (15%)	43 (13%)	39 (20%)
Pulmonary disease	43 (8%)	24 (7%)	19 (10%)
Vascular disease	91 (17%)	51 (15%)	40 (20%)
Connective tissue diseases	13 (2%)	9 (3%)	4 (2%)
Liver disease	34 (6%)	16 (5%)	18 (9%)
Kidney disease	42 (8%)	18 (5%)	24 (12%)
Diabetes	72 (13%)	42 (12%)	30 (15%)
Non-haematological cancer	51 (10%)	25 (7%)	26 (13%)
Type of haematological malignancy			
Myeloid neoplasms	175 (33%)	106 (31%)	69 (35%)
Myeloproliferative neoplasms	83 (15%)	56 (17%)	27 (14%)
Myelodysplastic syndromes	41 (8%)	21 (6%)	20 (10%)
Acute myeloid leukaemias	51 (10%)	29 (9%)	22 (11%)
Acute lymphoblastic leukaemias	16 (3%)	13 (4%)	3 (2%)
Hodgkin lymphoma	17 (3%)	14 (4%)	3 (2%)
Non-Hodgkin lymphomas	222 (41%)	138 (41%)	84 (42%)
Chronic lymphoproliferative neoplasms	69 (13%)	47 (14%)	22 (11%)
Indolent lymphomas	54 (10%)	33 (10%)	21 (11%)
Aggressive lymphomas	99 (18%)	58 (17%)	41 (21%)
Plasma cell neoplasms	106 (20%)	67 (20%)	39 (20%)
Time since haematological malignancy diagnosis, years	2 (0–6)	2 (0–6)	2 (0–5)
Time since last therapy for haematological malignancy, months	1 (0–12)	1 (0–12)	1 (0–13)
Haematological malignancy status: progressive disease	81 (15%)	33 (10%)	48 (24%)
COVID-19 disease severity			
Mild	268 (50%)	220 (65%)	48 (24%)
Severe	194 (36%)	106 (31%)	88 (44%)
Critical	74 (14%)	12 (4%)	62 (31%)

Data are n (%), median (IQR), or mean (SD).

Table 1: **Baseline characteristics and coexisting conditions by survival status**

(A B Federici MD); **Dipartimento di Medicina Specialistica, University of Udine, Udine,**

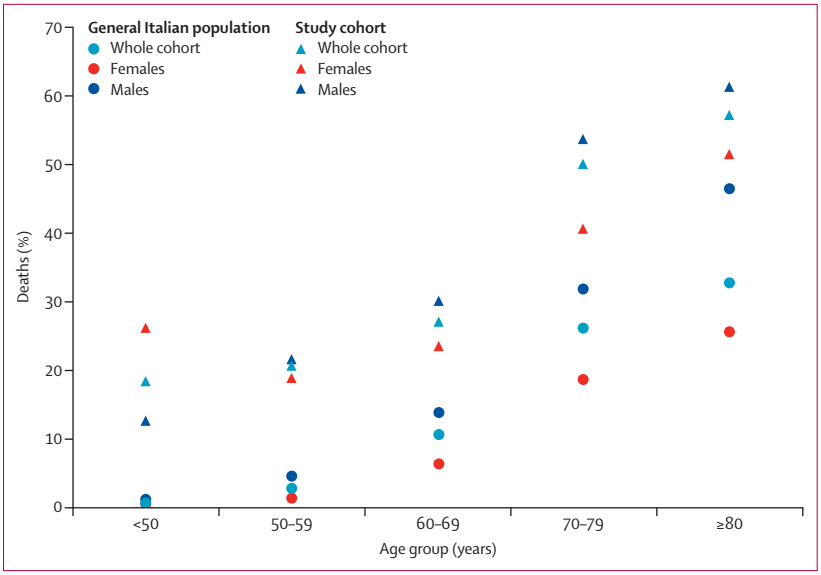

Figure 2: **COVID-19 mortality by age group in the study cohort and the general Italian population**

	Deaths/patients	Hazard ratio (95% CI)
Age (per year increase)	..	1·03 (1·01–1·05)
Sex		
Female	63/196	0·86 (0·60–1·24)
Male	135/340	1 (ref)
Charlson Comorbidity Index (per point increase)	..	1·06 (0·96–1·17)
Haematological malignancy status: progressive disease	48/81	2·10 (1·41–3·12)
Type of haematological malignancy		
Myeloproliferative neoplasms	27/83	1 (ref)
Myelodysplastic syndromes	20/41	1·58 (0·69–3·62)
Acute myeloid leukaemias	22/51	3·49 (1·56–7·81)
Acute lymphoblastic leukaemias	3/16	1·65 (0·46–5·94)
Hodgkin lymphomas	3/17	1·30 (0·36–4·66)
Chronic lymphoproliferative neoplasms	22/69	1·64 (0·77–3·51)
Indolent lymphomas	21/54	2·19 (1·07–4·48)
Aggressive lymphomas	41/99	2·56 (1·34–4·89)
Plasma cell neoplasms	39/106	2·48 (1·31–4·69)
Time since haematological malignancy diagnosis (per year increase)	..	1·01 (0·97–1·04)
Time since last therapy for haematological malignancy (per month increase)	..	1·00 (0·99–1·01)
COVID-19 disease severity		
Mild	48/268	1 (ref)
Severe or critical	150/268	4·08 (2·73–6·09)

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

Italy (A Candoni MD); **Hematology, Fondazione Policlinico Tor Vergata, Rome, Italy** (A Venditti MD); **Hematology, Istituto Nazionale Tumori IRCCS "Fondazione G Pascale", Naples, Italy** (A Pinto MD); **Hematology, Mazzoni Hospital, Ascoli Piceno, Italy** (P Galieni MD); **Hematology, Camillo-Forlanini Hospital, Rome, Italy** (L Rigacci MD); **Unit of Hematology, Stem Cell Transplantation, University Campus Bio-Medico, Rome, Italy** (D Armiento MD); **Department of Clinical Medicine and Surgery, Federico II Hospital, Naples, Italy** (Prof F Pane MD); **Dipartimento di Scienze Radiologiche ed Ematologiche, Fondazione Policlinico Universitario A Gemelli–IRCCS–Università Cattolica del Sacro Cuore, Rome, Italy** (L Pagano MD); **and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, University of Milano** (Prof P Corradini MD)

Correspondence to:
Prof Francesco Passamonti, Department of Medicine and Surgery, University of Insubria, 21100 Varese, Italy
francesco.passamonti@uninsubria.it

See Online for appendix

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 multiple myeloma, of whom eight (42%) died.

Discussion

In the COVID-19 pandemic, patients with haematological malignancies are potentially a high-risk population because of intrinsic frailty, immunosuppressive therapies, and frequent hospital visits for treatment delivery. In our study, 198 (37%) of 536 patients with haematological malignancies had died by data cutoff. Some smaller 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.[6] Mortality was 1·4% in a Chinese study including 926 patients with non-severe COVID-19,[6] 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)[4] and 21% in 5700 cases from the Northwell COVID-19 Research Consortium (14% of whom were admitted to the ICU).[3] In patients who received a solid organ transplantation, the mortality rate has been found to be around 20–30%.[24,25]

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 malignacies: dyspnoea occurred in 51% of patients (*vs* 17·3% in New York City[3] and 19% in China[6]) and fever in 75% of patients (*vs* 31% in New York City[3]). Mild symptoms such as headache and diarrhoea occurred in less than 10% of our hospitalised patients, similarly to the general population.[3,6] 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[13]). 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%).[11,13] 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

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.[10] 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.[11] 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

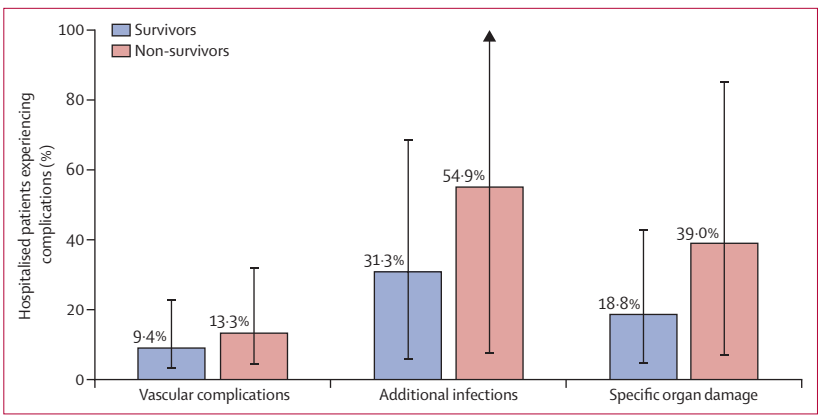

Figure 3: **Complications during hospitalisation among survivors and non-survivors**
Patients could have had multiple events.

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,[26] lopinavir–ritonavir,[27] or hydroxychloroquine.[28] 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.[29] 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,[30] 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.[31]

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 analysis 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, ABu, ACun, AR, NG, SG, AC, AMor, BF, ABi, FG, GV, MCT, AT, PT, FL, MasM, MT, FF, CG, LP, DV, MauM, ED, AG, ACo, ACuc, 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 lorenza.bertu@uninsubria.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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