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Age, Successive Waves, Immunization, and Mortality in Elderly COVID-19 Haematological Patients: EPICOVIDEHA Findings

Giuseppe ROSSI , Jon SALMANTON-GARCÍA , Chiara CATTANEO , Francesco MARCHESI , Julio DÁVILA-VALLS , Sonia MARTÍN-PÉREZ , Federico ITRI , Alberto LÓPEZ-GARCÍA , Andreas GLENTHØJ , Maria GOMES DA SILVA , Caroline BESSON , Monia MARCHETTI , Barbora WEINBERGEROVÁ , Ozren JAKSIC , Moraima JIMÉNEZ , Yavuz M. BILGIN , Jaap VAN DOESUM , Francesca FARINA , Pavel ŽÁK , Luisa VERGA , Graham P. COLLINS , Valentina BONUOMO , Jens VAN PRAET , Marcio NUCCI , Stef MEERS , Ildefonso ESPIGADO , Nicola S. FRACCHIOLLA , Toni VALKOVIĆ , Christian Bjørn POULSEN , Natasha ČOLOVIĆ , Giulia DRAGONETTI , Marie-Pierre LEDOUX , Carlo TASCINI , Caterina BUQUICCHIO , Ola BLENNOW , Francesco PASSAMONTI , Marina MACHADO , Jorge LABRADOR , Rafael F. DUARTE , Martin SCHÖNLEIN , Lucia PREZIOSO , Iker FALCES-ROMERO , Austin KULASEKARARAJ , Carolina GARCIA-VIDAL , Noemí FERNÁNDEZ , Ghaith ABU-ZEINAH , Irati ORMAZABAL-VÉLEZ , Tatjana ADŽIĆ-VUKIČEVIĆ , Klára PIUKOVICS , Igor STOMA , Annarosa CUCCARO , Gabriele MAGLIANO , Tomáš SZOTKOWSKI , Tomás-José GONZÁLEZ-LÓPEZ , Shaimaa EL-ASHWAH , Rui BERGANTIM , Uluhan SILI , Johan MAERTENS , Fatih DEMIRKAN , Cristina DE RAMÓN , Verena PETZER , Maria Ilaria DEL PRINCIPE , Milan NAVRÁTIL , Michelina DARGENIO , Guldane Cengiz SEVAL , Michail SAMARKOS , Zdeněk RÁČIL , László Imre PINCZÉS , Tobias LAHMER , Alessandro BUSCA , Gustavo-Adolfo MÉNDEZ , Antonio VENA , Monika M. BIERNAT , Maria MERELLI , Maria CALBACHO , Aleksandra BARAĆ , Martina BAVASTRO , Alessandro LIMONGELLI , Osman ILHAN , Dominik WOLF , Gökçe Melis ÇOLAK , Ramón GARCÍA-SANZ , Ziad EMARAH , Bojana MIŠKOVIĆ , Stefanie GRÄFE , Miloš MLADENOVIĆ , Tommaso Francesco AIELLO , Lucía NÚÑEZ-MARTÍN-BUITRAGO , Anna NORDLANDER , Elena ARELLANO , Giovanni Paolo Maria ZAMBROTTA , Emanuele AMMATUNA , Alba CABIRTA , Maria Vittoria SACCHI , Raquel NUNES RODRIGUES , Ditte Stampe HERSBY , Michaela HANAKOVA , Laman RAHIMLI , Raul CORDOBA , Oliver A. CORNELY , Livio PAGANO

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Highlights

- Largest sample of elderly COVID-19 and hematological malignancy patients
- Different severity of subsequent COVID-19 waves in different age groups
- Differences in malignancy and COVID-19 treatment within elderly
- Increasing age linked to mortality: 22% in the youngest to 38% in the eldest
- Pivotal importance of vaccination with at least three vaccine doses

Age, Successive Waves, Immunization, and Mortality in Elderly COVID-19 Haematological Patients: EPICOVIDEHA Findings

Short title

Characteristics and outcome of elderly hematologic patients with COVID-19

Authors

Giuseppe **ROSSI**, 1 * Jon **SALMANTON-GARCÍA**, 2 * Chiara **CATTANEO**, 3 Francesco **MARCHESI**, 4 Julio **DÁVILA-VALLS**, 5 Sonia **MARTÍN-PÉREZ**, 6 Federico **ITRI**, 7 Alberto **LÓPEZ-GARCÍA**, 8 Andreas **GLENTHØJ**, 9 Maria **GOMES DA SILVA**, 10 Caroline **BESSON**, 11 Monia **MARCHETTI**, 12 Barbora **WEINBERGEROVÁ**, 13 Ozren **JAKSIC**, 14 Moraima **JIMÉNEZ**, 15 Yavuz M. **BILGIN**, 16 Jaap **VAN DOESUM**, 17 Francesca **FARINA**, 18 Pavel **ŽÁK**, 19 Luisa **VERGA**, 20 Graham P. **COLLINS**, 21 Valentina **BONUOMO**, 22 Jens **VAN PRAET**, 23 Marcio **NUCCI**, 24 Stef **MEERS**, 25 Ildefonso **ESPIGADO**, 26 Nicola S. **FRACCHIOLLA**, 27 Toni **VALKOVIĆ**, 28 Christian Bjørn **POULSEN**, 29 Natasha **ČOLOVIĆ**, 30 Giulia **DRAGONETTI**, 31 Marie-Pierre **LEDOUX**, 32 Carlo **TASCINI**, 33 Caterina **BUQUICCHIO**, 34 Ola **BLENNOW**, 35 Francesco **PASSAMONTI**, 36 Marina **MACHADO**, 37 Jorge **LABRADOR**, 38 Rafael F. **DUARTE**, 39 Martin **SCHÖNLEIN**, 40 Lucia **PREZIOSO**, 41 Iker **FALCES-ROMERO**, 42 Austin **KULASEKARARAJ**, 43 Carolina **GARCIA-VIDAL**, 44 Noemí **FERNÁNDEZ**, 45 Ghaith **ABU-ZEINAH**, 46 Irati **ORMAZABAL-VÉLEZ**, 47 Tatjana **ADŽIĆ-VUKIČEVIĆ**, 48 Klára **PIUKOVICS**, 49 Igor **STOMA**, 50 Annarosa **CUCCARO**, 51 Gabriele **MAGLIANO**, 52 Tomáš **SZOTKOWSKI**, 53 Tomás-José **GONZÁLEZ-LÓPEZ**, 54 Shaimaa **EL-ASHWAH**, 55 Rui **BERGANTIM**, 56 Uluhan **SILI**, 57 Johan **MAERTENS**, 58 Fatih **DEMIRKAN**, 59 Cristina **DE RAMÓN**, 60 Verena **PETZER**, 61

Maria Ilaria **DEL PRINCIPE**, 62 Milan **NAVRÁTIL**, 63 Michelina **DARGENIO**, 64 Guldane Cengiz **SEVAL**, 65 Michail **SAMARKOS**, 66 Zdeněk **RÁČIL**, 67 László Imre **PINCZÉS**, 68 Tobias **LAHMER**, 69 Alessandro **BUSCA**, 70 Gustavo-Adolfo **MÉNDEZ**, 71 Antonio **VENA**, 72 Monika M. **BIERNAT**, 73 Maria **MERELLI**, 74 Maria **CALBACHO**, 75 Aleksandra **BARAĆ**, 76 Martina **BAVASTRO**, 77 Alessandro **LIMONGELLI**, 78 Osman **ILHAN**, 79 Dominik **WOLF**, 80 Gökçe Melis **ÇOLAK**, 81 Ramón **GARCÍA-SANZ**, 82 Ziad **EMARAH**, 83 Bojana **MIŠKOVIĆ**, 84 Stefanie **GRÄFE**, 85 Miloš **MLADENOVIĆ**, 86 Tommaso Francesco **AIELLO**, 87 Lucía **NÚÑEZ-MARTÍN-BUITRAGO**, 88 Anna **NORDLANDER**, 89 Elena **ARELLANO**, 90 Giovanni Paolo Maria **ZAMBROTTA**, 91 Emanuele **AMMATUNA**, 92 Alba **CABIRTA**, 93 Maria Vittoria **SACCHI**, 94 Raquel **NUNES RODRIGUES**, 95 Ditte Stampe **HERSBY**, 96 Michaela **HANAKOVA**, 97 Laman **RAHIMLI**, 98 Raul **CORDOBA**, 99 # Oliver A. **CORNELY**, 100 # Livio **PAGANO**, 101 #

* shared first authorship

shared last authorship

§ corresponding author

Affiliations

1. Hematology Unit, ASST-Spedali Civili, Brescia, Italy
2. University of Cologne, Faculty of Medicine, and University Hospital Cologne, Institute of Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany
   University of Cologne, Faculty of Medicine, University Hospital Cologne, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD) and Excellence Center for Medical Mycology (ECMM), Cologne, Germany
3. Hematology Unit, ASST-Spedali Civili, Brescia, Italy
4. Hematology and Stem Cell Transplant Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy
5. Hospital Nuestra Señora de Sonsoles, Ávila, Spain
6. Hospital Nuestra Señora de Sonsoles, Ávila, Spain
7. San Luigi Gonzaga Hospital - Orbassano, Orbassano, Italy
8. Fundacion Jimenez Diaz University Hospital, Health Research Institute IIS-FJD, Madrid, Spain
9. Department of Hematology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
10. Portuguese Institute of Oncology, Lisbon, Portugal
11. Centre Hospitalier de Versailles, Le Chesnay, France; Université Paris-Saclay, UVSQ, Inserm, Équipe "Exposome et Hérédité", CESP, Villejuif, France
12. Azienda Ospedaliera Nazionale SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy
13. Department of Internal Medicine - Hematology and Oncology, Masaryk University Hospital Brno, Brno, Czech Republic

14. Department of Hematology, University Hospital Dubrava, Zagreb, Croatia
15. Department of Hematology, Vacute lymphoid leukaemia d'Hebron Hospital Universitari, Experimental Hematology, Vacute lymphoid leukaemia d'Hebron Institute of Oncology (VHIO), Vacute lymphoid leukaemia d'Hebron Barcelona Hospital Campus, Barcelona, Spain
    Departament de Medicina, Universitat Autònoma de Barcelona, Bellaterra, Spain
16. Department of Internal Medicine, ADRZ, Goes, Netherlands
17. University Medical Center Groningen, Groningen, Netherlands
18. IRCCS Ospedale San Raffaele, Milan, Italy
19. University Hospital Hradec Králové, Hradec Králové, Czech Republic
20. Azienda Ospedaliera San Gerardo - Monza, Monza, Italy
    Università Milano-Bicocca, Milan, Italy
21. NIHR Oxford Biomedical Research Centre, Churchill Hospital, Oxford, United Kingdom
22. Department of Medicine, Section of Hematology, University of Verona, Verona, Italy
    Department of Clinical and Biological Sciences, University of Turin, Turin, Italy
23. Department of Nephrology and Infectious diseases, AZ Sint-Jan Brugge-Oostende AV, Brugge, Belgium
24. Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
25. AZ KLINA, Brasschaat, Belgium
26. Department of Hematology, University Hospital Virgen Macarena - University Hospital Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS / CSIC), Universidad de Sevilla (Departamento de Medicina), Seville, Spain
27. Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
28. University Hospital Centre Rijeka, Rijeka, Croatia
    Croatian Cooperative Group for Hematological Diseases (CROHEM)

Faculty of Medicine and Faculty of Health Studies University of Rijeka, Rijeka, Croatia

29. Zealand University Hospital, Roskilde, Roskilde, Denmark
30. University Clinical Center Serbia, Medical Faculty University Belgrade, Belgrade, Serbia
31. Hematology Unit, Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Rome, Italy
32. ICANS, Strasbourg, France
33. Azienda Sanitaria Universitaria del Friuli Centrale, Udine, Italy
34. Ematologia con Trapianto, Ospedale Dimiccoli Barletta, Barletta, Italy
35. Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden
36. Department of Medicine and Surgery, University of Insubria and ASST Sette Laghi, Ospedale di Circolo of Varese, Varese, Italy
37. Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain
38. Department of Hematology, Research Unit, Hospital Universitario de Burgos, Burgos, Spain
39. Hospital Universitario Puerta de Hierro, Majadahonda, Spain
40. Department of Oncology, Hematology and Bone Marrow Transplantation with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
41. Hospital University of Parma - Hematology and Bone Marrow Unit, Parma, Italy
42. La Paz University Hospital, Madrid, Spain

    CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain
43. King's College Hospital, London, United Kingdom

    King’s College London, London, United Kingdom

44. Hospital Clinic, Barcelona, Spain
45. Hospital Universitario Marqués de Valdecilla, Santander, Spain
46. Division of Hematology and Oncology, Weill Cornell Medicine, New York, United States
47. Complejo Hospitalario de Navarra, Iruña-Pamplona, Spain
48. COVID hospital "Batajnica", Belgrade, Serbia
49. Department of Internal Medicine, South Division Faculty of Medicine University of Szeged, Szeged, Hungary
50. Gomel State Medical University, Gomel, Belarus
51. Hematology Unit, Center for Translational Medicine, Azienda USL Toscana NordOvest, Livorno, Italy
52. ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
53. University Hospital Olomouc, Olomouc, Czech Republic
54. Department of Hematology, Hospital Universitario de Burgos, Burgos, Spain
55. Oncology Center, Mansoura University, Mansoura, Egypt
56. Centro Hospitalar e Universitário São João, Porto, Portugal
57. Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Marmara University, Istanbul, Turkey
58. Department of Microbiology, Immunology, and Transplantation, KULeuven, Leuven and Department of Hematology, UZ Leuven, Leuven, Belgium
59. Dokuz Eylul University, Division of Hematology, Izmir, Turkey
60. Hematology Department, Hospital Universitario de Salamanca, Salamanca, Spain IBSAL, Centro de Investigación del Cáncer-IBMCC (USAL-CSIC), Salamanca, Spain
61. Department of Hematology and Oncology, Medical University of Innsbruck, Innsbruck, Austria

62. Hematology, Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy
63. Head of the ICU and Transplant Unit, Department of Hematooncology, University Hospital of Ostrava, Ostrava-Poruba, Czech Republic
64. Hematology and Stem Cell transplan Unit, Vito Fazzi, Lecce
65. Ankara University, Ankara, Turkey
66. Laikon Hospital, Athens, Greece
67. Institute of Hematology and Blood Transfusion, Prague, Czech Republic
68. Division of Hematology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
69. Medizinische Klinik II, Klinikum rechts der Isar, TU München, Munich, Germany
70. Stem Cell Transplant Center, AOU Citta' della Salute e della Scienza, Turin, Italy
71. Hospital Escuela de Agudos Dr. Ramón Madariaga, Posadas, Argentina
72. IRCCS AOU San Martino (IRCCS Ospedale Policlinico San Martino), Genova, Italia
73. Department of Haematology, Blood Neoplasms, and Bone Marrow Transplantation, Wroclaw Medical University, Wroclaw, Poland
74. Azienda Sanitaria Universitaria del Friuli Centrale, Udine, Italy
75. Hospital Universitario 12 de Octubre, Madrid, Spain
76. Clinic of Hematology, Clinical Center of Serbia, Belgrade, Serbia
77. IRCCS AOU San Martino (IRCCS Ospedale Policlinico San Martino), Genova, Italia
78. IRCCS AOU San Martino (IRCCS Ospedale Policlinico San Martino), Genova, Italia
79. Ankara University, Ankara, Turkey
80. Department of Hematology and Oncology, Medical University of Innsbruck, Innsbruck, Austria
81. Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Marmara University, Istanbul, Turkey

82. Head of Molecular Biology an HLA Unit, Department of Hematology, University Hospital of Salamanca (HUS/IBSAL/CIBERONC), Salamanca, Spain

IBSAL, Centro de Investigación del Cáncer-IBMCC (USAL-CSIC), Salamanca, Spain

83. Oncology Center, Mansoura University, Mansoura, Egypt

84. COVID hospital ""Batajnica"", Belgrade, Serbia

Clinic for Orthopedic Surgery and Traumatology, University Clinical Center of Serbia, Belgrade, Serbia

85. I. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

III. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

University of Cologne, Faculty of Medicine, and University Hospital Cologne, Institute of Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany

University of Cologne, Faculty of Medicine, University Hospital Cologne, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD) and Excellence Center for Medical Mycology (ECMM), Cologne, Germany

86. COVID hospital ""Batajnica"", Belgrade, Serbia

Clinic for Orthopedic Surgery and Traumatology, University Clinical Center of Serbia, Belgrade, Serbia

87. Hospital Clinic, Barcelona, Spain

88. Hospital Universitario Puerta de Hierro, Majadahonda, Spain

89. Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden

90. Department of Hematology, University Hospital Virgen Macarena - University Hospital Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS / CSIC), Universidad de Sevilla (Departamento de Medicina), Seville, Spain
91. Azienda Ospedaliera San Gerardo - Monza, Monza, Italy
Università Milano-Bicocca, Milan, Italy
92. University Medical Center Groningen, Groningen, Netherlands
93. Department of Hematology, Vacute lymphoid leukaemia d'Hebron Hospital Universitari, Experimental Hematology, Vacute lymphoid leukaemia d'Hebron Institute of Oncology (VHIO), Vacute lymphoid leukaemia d'Hebron Barcelona Hospital Campus, Barcelona, Spain
94. Azienda Ospedaliera Nazionale SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy
95. Portuguese Institute of Oncology, Lisbon, Portugal
96. Department of Hematology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
97. Institute of Hematology and Blood Transfusion, Prague, Czech Republic
98. University of Cologne, Faculty of Medicine, and University Hospital Cologne, Institute of Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany
University of Cologne, Faculty of Medicine, University Hospital Cologne, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD) and Excellence Center for Medical Mycology (ECMM), Cologne, Germany
99. Fundacion Jimenez Diaz University Hospital, Health Research Institute IIS-FJD, Madrid, Spain

100. University of Cologne, Faculty of Medicine, and University Hospital Cologne, Institute of Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany

University of Cologne, Faculty of Medicine, University Hospital Cologne, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD) and Excellence Center for Medical Mycology (ECMM), Cologne, Germany

University of Cologne, Faculty of Medicine, and University Hospital Cologne, Clinical Trials Centre Cologne (ZKS Köln), Cologne, Germany

University of Cologne, Faculty of Medicine, and University Hospital Cologne, Center for Molecular Medicine Cologne (CMMC), Cologne, Germany

German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany

101. Hematology Unit, Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Rome, Italy

Hematology Unit, Università Cattolica del Sacro Cuore, Rome, Italy

ORCID number

Giuseppe ROSSI	0000-0001-8377-2898
Jon SALMANTON-GARCÍA	0000-0002-6766-8297
Chiara CATTANEO	0000-0003-0031-3237
Francesco MARCHESI	0000-0001-6353-2272
Julio DÁVILA-VALLS	0000-0002-5185-2073
Sonia MARTÍN-PÉREZ	0000-0001-5809-7165
Federico ITRI	0000-0002-3532-5281
Alberto LÓPEZ-GARCÍA	0000-0002-5354-5261
Andreas GLENTHØJ	0000-0003-2082-0738
Maria GOMES DA SILVA	0000-0002-6993-2450
Caroline BESSON	0000-0003-4364-7173
Monia MARCHETTI	0000-0001-7615-0572
Barbora WEINBERGEROVÁ	0000-0001-6460-2471
Ozren JAKSIC	0000-0003-4026-285X
Moraima JIMÉNEZ	0000-0003-1444-8562
Yavuz M. BILGIN	0000-0002-3783-3407
Jaap VAN DOESUM	0000-0003-0214-3219
Francesca FARINA	0000-0002-5124-6970
Pavel ŽÁK	0000-0003-4465-5343
Luisa VERGA	0000-0002-0868-3358
Graham P. COLLINS	0000-0002-8803-4234
Valentina BONUOMO	0000-0001-6491-8337
Jens VAN PRAET	0000-0002-7125-7001
Marcio NUCCI	0000-0003-4867-0014
Stef MEERS	0000-0003-1754-2175
Ildefonso ESPIGADO	0000-0002-4043-6613
Nicola S. FRACCHIOLLA	0000-0002-8982-8079
Toni VALKOVIĆ	0000-0001-6083-8815
Christian Bjørn POULSEN	0000-0001-9785-1378
Natasha ČOLOVIĆ	0000-0002-1321-4812
Giulia DRAGONETTI	0000-0003-1775-6333
Marie-Pierre LEDOUX	0000-0002-3261-3616
Carlo TASCINI	0000-0001-9625-6024
Caterina BUQUICCHIO	0000-0002-3683-5953
Ola BLENNOW	0000-0002-7167-7882
Francesco PASSAMONTI	0000-0001-8068-5289
Marina MACHADO	0000-0002-8370-2248
Jorge LABRADOR	0000-0002-3696-0287
Martin SCHÖNLEIN	0000-0002-1010-0975
Lucia PREZIOSO	0000-0003-1660-4960
Iker FALCES-ROMERO	0000-0001-5888-7706
Austin KULASEKARARAJ	0000-0003-3180-3570
Carolina GARCIA-VIDAL	0000-0002-8915-0683
Ghaith ABU-ZEINAH	0000-0002-1881-3670
Irati ORMAZABAL-VÉLEZ	0000-0003-1141-5546
Klára PIUKOVICS	0000-0003-4480-3131
Igor STOMA	0000-0003-0483-7329
Annarosa CUCCARO	0000-0002-0237-1839

Gabriele MAGLIANO	0000-0002-9129-1530
Tomás José GONZÁLEZ-LÓPEZ	0000-0003-2458-2554
Shaimaa EL-ASHWAH	0000-0003-2210-1534
Rui BERGANTIM	0000-0002-7811-9509
Uluhan SILI	0000-0002-9939-9298
Johan MAERTENS	0000-0003-4257-5980
Fatih DEMIRKAN	0000-0002-1172-8668
Cristina DE RAMÓN	0000-0002-8167-6410
Verena PETZER	0000-0002-9205-1440
Maria Ilaria DEL PRINCIPE	0000-0002-3958-0669
Milan NAVRÁTIL	0000-0002-2067-1253
Michelina DARGENIO	0000-0003-0924-4629
Guldane Cengiz SEVAL	0000-0001-9433-2054
Michail SAMARKOS	0000-0001-9630-9712
Zdeněk RÁČIL	0000-0003-3511-4596
László Imre PINCZÉS	0000-0003-0453-1709
Tobias LAHMER	0000-0003-1008-5311
Alessandro BUSCA	0000-0001-5361-5613
Gustavo-Adolfo MÉNDEZ	0000-0003-0514-7004
Antonio VENA	0000-0002-0697-3992
Monika M. BIERNAT	0000-0003-3161-3398
Maria MERELLI	0000-0003-3352-1163
Maria CALBACHO	0000-0001-8106-4863
Aleksandra BARAĆ	0000-0002-0132-2277
Martina BAVASTRO	0000-0003-1780-0920
Alessandro LIMONGELLI	0000-0001-7995-5528
Osman ILHAN	0000-0003-1665-372X
Dominik WOLF	0000-0002-4761-075X
Gökçe Melis ÇOLAK	0000-0002-7662-7454
Ramón GARCÍA-SANZ	0000-0003-4120-2787
Ziad EMARAH	0000-0003-0622-2598
Bojana MIŠKOVIĆ	0000-0002-6585-6227
Stefanie GRÄFE	0000-0001-7678-0179
Miloš MLADENOVIĆ	0000-0002-8350-2182
Tommaso Francesco AIELLO	0000-0002-8915-0683
Elena ARELLANO	0000-0003-0581-8947
Giovanni Paolo Maria ZAMBROTTA	0000-0002-8612-2994
Emanuele AMMATUNA	0000-0001-8247-4901
Alba CABIRTA	0000-0001-7198-8894
Maria Vittoria SACCHI	0000-0001-8133-3357
Raquel NUNES RODRIGUES	0000-0002-8347-4281
Ditte Stampe HERSBY	0000-0002-2999-8949
Laman RAHIMLI	0000-0003-2266-445X
Oliver A. CORNELY	0000-0001-9599-3137
Raul CORDOBA	0000-0002-7654-8836
Livio PAGANO	0000-0001-8287-928X

Collaborators (to be mentioned in PubMed)

Joyce **MARQUES DE ALMEIDA**, José-Ángel **HERNÁNDEZ-RIVAS**, Anna **GUIDETTI**, Olimpia **FINIZIO**, Zlate **STOJANOSKI**, Milche **CVETANOSKI**, Joseph **MELETIADIS**, Nick **DE JONGE**, Darko **ANTIĆ**, Natasha **ALI**, Maria Chiara **TISI**, Laura **SERRANO**, Gaëtan **PLANTEFEVE**, Nina **KHANNA**, Martin **HOENIGL**, Martin **ČERŇAN**, Carolina **MIRANDA-CASTILLO**, María **FERNÁNDEZ-GALÁN**, Alexandra **SERRIS**, Nurettin **ERBEN**, Rémy **DULÉRY**, Avinash **AUJAYEB**, Mario Virgilio **PAPA**, Jan **NOVÁK**, Mario **DELIA**, Giuseppe **SAPIENZA**, Florian **REIZINE**, Ali S. **OMRANI**, Roberta **DI BLASI**, Sylvain **LAMURE**, Ľuboš **DRGOŇA**, Nicola **COPPOLA**, Josip **BATINIĆ**, Murtadha **AL-KHABORI**, José-María **RIBERA-SANTA SUSANA**, Monica **PIEDIMONTE**, Jorge **LOUREIRO-AMIGO**, Guillemette **FOUQUET**, Rita **FAZZI**, François **DANION**, Jörg **SCHUBERT**, Baerbel **HOELL-NEUGEBAUER**, Nathan C. **BAHR**, Ayel Omar **YAHIA**, Ana **TORRES-ATIENZA**, Ikhwan **RINALDI**, Marina **POPOVA**, Hans-Beier **OMMEN**, Maria Enza **MITRA**, Malgorzata **MIKULSKA**, Ira **LACEJ**, Sofya **KHOSTELIDI**, Sein **WIN**, Donald **VINH**, Modar **SALEH**, Juergen **PRATTES**, Pavel **JINDRA**, Fabio **GUOLO**, Roberta **DELLA PEPA**, Ekaterina **CHELYSHEVA**, Przemyslaw **ZDZIARSKI**, Vivien **WAI-MAN**, Andrés **SOTO-SILVA**, Hans Martin **ORTH**, Sandra **MALAK**, Lisset **LORENZO DE LA PEÑA**, Martin **KOLDITZ**, Chi Shan **KHO**, Christopher H. **HEATH**, Ana **GROH**, Eleni **GAVRIILAKI**, Monica **FUNG**, Matthias **EGGER**, Elizabeth **DE KORT**, Erik **DE CABO**, Tania **CUSHION**, Fazle Rabbi **CHOWDHURY**, M. Mansour **CEESAY**, Mathias **BREHON**, Gina **VARRICCHIO**, Agostino **TAFURI**, María-Josefa **JIMÉNEZ-LORENZO**, Nikolai **KLIMKO**, Panagiotis **TSIRIGOTIS**, Anastasia **ANTONIADOU**, Maria **VEHRESCHILD**

Corresponding author

Dr. Jon Salmanton-García

University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany and Department I of Internal Medicine, Excellence Center for Medical Mycology (ECMM)

Herderstraße 52-54 50931 Cologne, Germany

Phone: +49 221 478 85523 | Fax: +49 221 478 1421445

E-mail: jon.salmanton-garcia@uk-koeln.de

Abstract

Introduction

Elderly patients with haematologic malignancies face the highest risk of severe COVID-19 outcomes. The infection impact in different age groups remains unstudied in detail.

Methods

We analysed elderly patients (age groups: 65-70, 71-75, 76-80 and >80 years old) with hematologic malignancies included in the EPICOVIDEHA registry between January 2020 and July 2022. Univariable and multivariable Cox regression models were conducted to identify factors influencing death in COVID-19 patients with haematological malignancy.

Results

The study included data from 3,603 elderly patients (aged 65 or older) with haematological malignancy, with a majority being male (58.1%) and a significant proportion having comorbidities. The patients were divided into four age groups, and the analysis assessed COVID-19 outcomes, vaccination status, and other variables in relation to age and pandemic waves. The 90-day survival rate for patients with COVID-19 was 71.2%, with significant differences between groups. The pandemic waves had varying impacts, with the first wave affecting patients over 80 years old, the second being more severe in 65-70, and the third being the least severe in all age groups. Factors contributing to 90-day mortality included age, comorbidities, lymphopenia, active malignancy, acute leukaemia, less than three vaccine doses, severe COVID-19, and using only corticosteroids as treatment.

Conclusions

These data underscore the heterogeneity of elderly haematological patients, highlight the different impact of COVID waves and the pivotal importance of vaccination, and may help in planning future healthcare efforts.

Introduction

The impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has caused excess mortality worldwide. Its severity and clinical consequences varied according to differences in the characteristics of infected subjects. Both, age [1] and hematologic malignancy [2-17] proved to be adverse prognostic factors in most studies reported, making elderly patients affected by haematological malignancy among the categories of patients most vulnerable to severe infection. A better knowledge of the clinical characteristics of coronavirus disease 2019 (COVID-19) [18] together with the availability of effective prophylactic and therapeutic agents and the benefits of widespread vaccination policies have allowed a progressive improvement of COVID-19 prognosis.

To which extent the improvement in COVID-19 prognosis and the efficacy of prophylactic interventions affects elderly patients with haematological malignancy is only partially known [9]. Also, differences in the viral strain involved [2, 19-21] and in vaccination status [12, 14, 15, 19] likely influence the risk of COVID-19 progression to severe episodes among elderly hematologic patients. The potential role of differences in the age of elderly patients with haematological malignancy on the outcome of COVID-19 and their relationship with other prognostic variables have been only partially analysed, including time of infection [5], viral strain [2, 19-21], vaccination status [12, 14, 15, 19], and hematologic diagnosis [3, 4, 6-8, 10, 11, 17].

This analysis was conducted by the collaboration of the EPICOVIDEHA registry [22] from the European Hematology Association (EHA) Infections in Hematology Scientific Working Group (SWG) and the EHA Hematology and Aging SWG. The characteristics of patients aged >65 with haematological malignancy developing COVID-19 throughout different periods of the pandemic, have been analysed in detail. Results may provide scientific

knowledge useful for improved management of elderly patients and for adopting rationale interventions to face the tasks which the pandemic may present in the future. The aim of this study is to assess the impact of age, vaccination status, viral strain, and other variables on the prognosis of elderly patients with hematological malignancy who contracted COVID-19 during different phases of the pandemic, addressing a critical gap in knowledge regarding the optimal management of this vulnerable population.

Methods

Patients aged ≥65 registered in the EPICOVIDEHA registry [22] between March 2020 and July 31st 2022, were included into the present analysis. They were divided in four groups according to the following age ranges: 65-70 years, 71-75 years, 76-80 years, and >80 years. Additionally, the patients included to analysis had to have a laboratory-based diagnosis of COVID-19 and a documented history of active hematological malignancy within the last 5 years before COVID-19 diagnosis for participation in this study.

In addition to age, other variables were collected: sex, comorbidities, diagnosis of haematological malignancy, malignancy status at COVID-19 onset and last haematological treatment received before COVID-19 diagnosis, neutrophil and lymphocyte count at COVID-19 onset, number and type of vaccine doses received, timing of COVID-19 diagnosis subdivided according to the following pandemic waves: 1st wave from January to April 2020, 2nd wave from September 2020 to March 2021, 3rd wave from September 2021 to March 2022 and 4th wave from May to July 2022. Furthermore, COVID-19 aetiology, clinical severity, need for hospitalization and ICU admission, treatment, death, and cause of death were also documented.

Categorical variables are presented as frequencies and percentages and continuous variables as median, interquartile range (IQR) and absolute range. A univariable Cox regression model was built and run with variables expected to play a role in mortality in haematological malignancy patients with COVID-19. Variables with a P value ≤0.1 were included in the multivariablee analysis. The multivariable Cox regression model was calculated using the Wald backward method. Survival probability was verified with Kaplan-Meier survival curves. Log-rank test was used to compare the survival probabilities of patients included in the different models. A P value ≤0.05 was considered statistically

significant. SPSS version 25.0 was used for statistical analysis (SPSS, IBM Corp, Chicago, IL, United States).

Results

A total of 3603 patients registered in the EPICOVIDEHA registry were studied. Median age was 74 years (IQR 70-80; absolute range 65-97). Males represented 58.1% (n=2093/3603) of cases. Only 25.2% (n=909/3603) of the patients had no comorbidities. Increasing age negatively correlated with the proportion of patients without comorbidities from 30.6% (n=319/1044) in patients aged 65-70 to 20.0% (n=164/819) in patients aged >80 (p<0.001). The coexistence of three or more comorbidities increased with age from 12.3% (n=128/1044) in patients aged 65-70 to 22.7% (n=186/819) in patients >80 years old. Cardiac (p=0.001) and renal (p<0.001) comorbidities showed the same increasing trend, whereas the frequency of obesity (p=0.004) and a history of smoking (p=0.003) was progressively decreasing from the youngest to the eldest age group (Table 1).

Myelodysplastic syndrome was the only haematologic malignancy correlating with age (p=0.001). Its frequency increased from 6.5% (n=68/1044) in patients aged 65-70 to 17.3% (n=142/819) in patients aged >80. Most patients (n=3059/3603, 84.9%) had received some treatment for their baseline haematological malignancy, which was active in 32.9% (n=1186/3603) of patients at COVID-19 diagnosis. The proportion of patients receiving no treatment (n=181/819, 22.1%), treatment with demethylating agents (n=67/819, 8.2%), or best supportive/palliative care (n=61/819, 7.4%) was highest above 80 years of age, whereas the proportion of patients treated with immunochemotherapy was lowest (n=168/819, 20.5%, p=0.001). Allogeneic or autologous stem cell transplants had been performed only in patients under the age of 75, while two patients aged 75-80 years had been treated with chimeric antigen receptor T-cell (CAR-T) cells. Peripheral blood cell counts showed severe neutropenia (absolute neutrophil count $<0.5x10^9$/L) in 7.1% (n=256/3603) and lymphopenia (lymphocyte count $<0.2/10^9$/L) in 9.3% (n=334/3603) of

cases. Both, severe neutropenia (p=0.017) and lymphopenia (p=0.001) were more pronounced in patients aged 65-70 and decreased in elder age groups (Table 1).

The first wave affected particularly the eldest age groups (75+ years) whereas the second wave the youngest (65-75 years, p<0.001). No further differences were observed during the subsequent pandemic waves. The viral strain causing COVID-19 was identified in 19.6% (n=706/3603) of patients, with the Omicron variant accounting for COVID-19 aetiology in 12.1% (n=437/3603). Before developing COVID-19, 31.5% of patients had received at least one vaccine dose, in 90.6% (n=1025/1135) of the cases with a messenger ribonucleic acid (mRNA) vaccine. Many patients had received two (n=442/3603, 12.3%) or three doses (n=570/3603, 15.8%). Severe or critical infection was experienced by 58.5% (n=2109/3603) of the patients. Vaccination rates did not change significantly with increasing age (p=0.172, Table 1).

The frequency of COVID-19 diagnosis during screening was lower in the eldest patients (p=0.010). Hospitalization was needed by 73.2% (n=2638/3603) of the patients and intensive care required by 21.2% (n=560/3603). COVID-19 was gradually more severe based on the age of the patient, requiring more frequent hospitalization and reporting more often pulmonary symptoms at increasing age (p<0.001). The eldest patients were less commonly admitted to ICU (p<0.001). Potential treatment for COVID-19 was collected from 51.7% (n=1864/3603) of the patients. One fifth (n=752/3603, 20.9%) of the patients did not get any treatment, and between those receiving any drug, corticosteroids alone were the most prevalent (n=385/3603, 10.7%, Table 1).

At day 30 post COVID-19 diagnosis, 23.6% (n=852/3603) had died; (n=1038/3603), this rose to 28.8% at day 90 (Table 2). The mortality rate raised at one year to 30.4%

(n=1095/3603). At day 90, mortality rate was 21.9% (n=229/1044) in patients aged 65-70, 26.2% (n=244/932) in those aged 71-75, 31.1% (n=251/808) in those aged 76-80 and 38.3% (n=314/819) in those aged >80, respectively. In the survival probability analysis, a statistically significant difference was observed (p<0.001), with an aged-based gradient from younger to elder patients (Figure 1A). COVID-19 was involved in the overall mortality in 91.9% (n=753/1107) of patients; haematologic malignancy contributed in 23.8% (n=264/1107). These proportions did not differ in the different age groups (p=0.755, Table 2).

The 90-day mortality rate was markedly higher in patients diagnosed of COVID-19 during the first wave of the pandemic (n=374/820 45.6%) than in the second (n=385/1198, 37.3%, p<0.001). Day-90 mortality dropped significantly for patients diagnosed during the third wave (n=178/1055, 16.9%, p<0.001). During the first wave, the 90-day mortality rate of patients aged 65-70 was 29.7% (n=310/1044) and it progressively increased in the elder groups, being 39.6% (n=369/932) in those aged 71-75, 48.7% (n=393/808) in those aged 76-80 and 60.1% (n=492/819) in those aged >80 (p<0.001). Conversely, the increase in 90-day mortality from the youngest to the eldest age group was less marked during the second wave (27.9% (n=291/1044) in patients aged 65-70 and 41.0% (n=336/819) in patients aged >80, p<0.001). Association between the age of the patients and the pandemic wave was also observed in the survival probability analysis (p<0.001, Figure 1B, Figure 2A, Supplementary table 1).

Vaccination status and number of vaccine doses received significantly impacted on survival probability at 90-day (p<0.001), which progressively increased among patients receiving zero, one, two, three or four doses, with differences being statistically significant for each pairwise comparison between groups (Supplementary table 1).

Considering patients whose viral strain was genotyped, those with wild-type, alpha or delta variants, had a comparable survival probability at day 90, although significantly worse than in patients with omicron variant (p<0.001, Figure 1C).

The 90-day mortality in patients receiving only corticosteroids was 35.6% (n=137/385. In patients receiving antivirals with or without other treatments, 90-day mortality was significantly lower (n=126/438, 25.7%) and in those receiving only monoclonal antibodies with or without other treatments it was 12.5% (n=32/255, p<0.001, Figure 2B, Supplementary table 1).

In the multivariable regression analysis (Table 3), age was a significant independent risk factor for 90-day mortality. The presence of a cardiac (hazard ratio [HR] 1.262, 95% confidence interval [CI] 1.107-1.438), hepatic (HR 1.573, 95% CI 1.204-2.054) or renal (HR 1.233, 95% CI 1.029-1.476) comorbidity had significantly negative impact on patient outcome, as well as lymphopenia at COVID-19 diagnosis. Acute leukaemia had a significantly worse prognosis than any other malignancy. Moreover, an active hematologic malignancy at COVID-19 diagnosis (HR 1.651, 95% CI 1.421-1.918) also had an adverse impact on patient survival, so did baseline pulmonary involvement and critical COVID-19 (HR 2.903, 95% CI 2.517-3.347). Among COVID-19 treatments, receiving only corticosteroids increased the risk of death (HR 1.407, 95% CI 1.077-1.837), whereas the incorporation of monoclonal antibodies significantly decreased it (HR 0.589, 95% CI 0.380-0.915). In patients >80 years old, male sex also had significantly worse prognosis (HR 1.355, 95% CI 1.074-1.709).

Discussion

Increased age was the most frequent independent risk factor for an adverse outcome of COVID-19 reported in patients with haematological malignancy. In the present study the large number patients analysed allowed to demonstrate the negative impact of increasing age even in the elderly population and to dissect the prognosis of COVID-19 according to clinical and therapeutic variables. More importantly, the duration of the study encompassing three pandemic waves from January 2020 to March 2022 enabled to show that prognosis gradually improved, particularly during the third wave mainly sustained by the Omicron variant and that receiving three doses of vaccine further ameliorated patient's survival.

The present study confirms that chronological age significantly worsens the outcome of COVID-19 even within a population of haematological malignancy selected for age ≥65 years, whose median age was 74. Overall, the 90-day survival was 71.2% and survival rates decreased with age. Survival differences were significant between each 5-year group, underscoring the prominent importance of chronological age as a predictor of adverse outcome, even within subjects collectively defined as advanced age. In previous research, age was a significant adverse prognostic factor in 19 of 25 worldwide epidemiological studies analysed [23]. None of those studies evaluated the impact of increasing age specifically within the elderly patient population. However, some insights have emerged from a meta-analysis involving over 600,000 patients that specifically assessed the impact of advancing age on mortality within the elderly demographic [24].

The characteristics of elderly patients studied were similar to those of patients with haematological malignancy and COVID-19 of any age reported in larger studies. As expected, the frequency of comorbidities, particularly cardiac, was higher, and there were relatively more patients with chronic lymphoid leukaemia and myelodysplastic syndrome

and less with acute lymphoid leukaemia, chronic myeloid leukaemia and Hodgkin's lymphoma, reflecting the epidemiology of the general population.

In our elderly patients, there were significant differences associated with increasing age in variables potentially impacting survival. The eldest patients had more comorbidities but less severe neutropenia and lymphopenia. More importantly, they were less likely to receive targeted antivirals and monoclonal antibodies for COVID-19, or to receive intensive care when hospitalized for severe disease. Nevertheless, multivariable analysis confirmed that age *per se* remains one of the most powerful independent predictors of adverse outcome among elderly patients with COVID-19.

The role of haematological malignancy as a direct cause of death was limited, accounting for only 8.1% of deceased patients. This proportion was lower than that reported in haematological malignancy patients of any age suggesting that in elderly persons the clinical impact of COVID-19 was more severe than that of their underlying haematological malignancy [12-14, 18, 19]. Among the different haematological malignancies, the prognosis of COVID-19 was worst in patients with acute leukaemia, where increasing age had a negative prognostic effect. In other haematological malignancies this effect was less pronounced.

Similarly to the general population, the first wave of COVID-19 from January to April 2020 was more severe than the second from September 2020 to March 2021, which in turn was more severe than the third wave, from September 2021 to march 2022. The severity of COVID-19 during the first wave was particularly evident in patients >80 years old who were the largest group and whose 90-day survival did not reach 40%. On the contrary, the second wave affected primarily the youngest age group whose outcome did not differ from the first wave, whereas in the other age groups COVID-19 burden gradually decreased and its outcome improved. The third pandemic wave did not show an age predominance

within elderly patients and its prognosis was markedly better with death rates below 20% in all age groups including patients >80 years old.

The improved outcome of COVID-19, in parallel to the pandemic evolution, has been ascribed to a presumed lower virulence of the omicron virus variant [2, 19-21], mostly represented since the third wave of the pandemic. However, in haematological malignancy patients, omicron was still associated with considerable attributable mortality [19]. Although the viral strain was known only in a limited number of patients, the present study confirms that survival with the omicron variant was significantly higher also in elderly patients. The increased survival rates were particularly evident in patients aged 65-70 whereas in the elder groups, differences between omicron and the other variants were less notable, suggesting that if a patient is frail due to coexisting conditions like haematological malignancy, the effects of the lower virulence of virus variant may be outbalanced by increasing age.

The vaccination status may have also played a substantial role in the better outcome of the more recent omicron variants. An improvement both on 30-day and on 90-day survival was documented in patients receiving at least one dose of vaccine compared to unvaccinated patients. The difference was highly significant despite a low vaccination rate. This result may be surprising as it is generally assumed that haematological malignancy is associated with a lack of serological response to vaccines, both against COVID or other viruses, for example influenza [25]. In addition, treatments commonly used in haematological malignancy, like anti-CD20 monoclonal antibodies and Bruton's tyrosine kinase (BTK) inhibitors [7], are strong inhibitors of anti-SARS-CoV-2 antibody production after vaccination [26, 27], and increasing age may contribute to a reduced response to vaccination in haematological malignancy [26], as reported already, with an age cut-off of 82 years, but not in other reports [27]. Nevertheless, our report strongly documents the paramount importance of vaccination in elderly patients with haematological malignancy

as well as the increasingly favourable impact of vaccination in parallel to increasing age. The beneficial effect of vaccines was magnified by the worsening prognosis with increasing age of unvaccinated patients. In patients >80 years old, a single vaccine dose was sufficient to improve survival significantly compared to unvaccinated persons, whose 90-day survival was lower than 50%. Patients aged 75-80 required a two-dose vaccination course to have a significant survival advantage, while a third additional dose was necessary in the cohort of patients aged 71-75. Similarly, in patients aged 65-70, a third dose was associated with a marked survival improvement compared to receiving only two doses.

The efficacy of a booster dose in enhancing the serological response rate and also the cellular immune response in persistently seronegative patients has been already reported in patients with haematological malignancy, irrespective of age [28], except in those recently treated with anti-CD20 monoclonal antibodies [29]. In the present study, the importance of a third vaccine dose in elderly patients was further highlighted by the multivariable analysis showing that vaccination with three doses was the most important actionable variable conferring an independent survival advantage. A lower number of doses and infection with the omicron virus variant did not reach statistical significance.

The potential further benefit of a fourth vaccine dose in haematological malignancy patients is still under investigation. In a small series of solid organ transplant patients, a 50% seroconversion of seronegative patients and a 100% boosting of patients with low-positive antibody levels was shown [30]. Results of the present series are to be interpreted with caution since only 42 patients had received a fourth vaccine dose. Nevertheless, survival of these patients at 90-day reached over 90% overall and 100% in those aged 65-70 and 75-80, and it was consistently better than that of patients receiving three doses in all age groups.

Taken together, these data highlight the key importance of vaccination in a category of patients with a combination of multiple risk factors like comorbidities and haematological malignancy, whose difficulties in coping with COVID-19 are magnified by the increase in chronological age. Of note, age was recently demonstrated as the most significant adverse risk factor for survival in vaccinated patients with breakthrough COVID-19 [12, 14]. Therefore, every improvement in the ability to effectively respond to the virus, including the immune response to multiple doses of vaccine, should be actively pursued.

In multivariable analysis, also an active hematologic malignancy, a diagnosis of acute leukaemia, a more severe presentation of COVID-19, as well as comorbidities and severe lymphopenia were independently associated with mortality. They have been reported as potential risk factors in other reports on adult haematological malignancy patients with COVID-19 [31]. Unlike vaccination, most of these variables can be hardly addressed to improve the prognosis of our patients. However, the use of prolonged treatments for haematological malignancy, potentially causing lymphopenia, as well as an optimal management of cardiac, renal, and hepatic comorbidities should be implemented to limit the dismal consequences of COVID-19 in elderly patients with haematological malignancy. Our data show that increasing age was associated with a suboptimal management of COVID-19. The use of antivirals and monoclonal antibodies, whose efficacy was highlighted also in our series, was apparently neglected particularly in patients >80 years old, although in this category of very frail patients better infection management may maximize therapeutic benefits.

This large registry study has some limitations in addition to its retrospective nature. Data are incomplete particularly regarding identification of SARS-CoV-2 variants, COVID-19 treatments, and potential thromboembolic phenomena. Other relevant limitations include the absence of sample size calculation due to its exploratory aims, and the potential bias stemming from the lack of data on functionality, cognition, and the prevalence of

polypharmacy among the elderly patients with haematological malignancy who contracted COVID-19, which could have provided additional insights into their overall health status and outcomes. Finally, the fact that antiviral and monoclonal antibody treatments were underutilized in patients over 80, potentially limiting benefits in this vulnerable group.

In conclusion, elderly COVID-19 patients with haematological malignancy are a heterogeneous group whose prognosis markedly worsens with age. Despite the above limitations, the data collected provide a framework to address the optimal healthcare management of elderly haematological malignancy patients using preventive and therapeutic strategies, including vaccination and antiviral agents, which may be modulated according to increasing chronological age. Additionally, this study underscores the significant impact of age on the prognosis of elderly COVID-19 patients with haematological malignancy, mirroring the worse vital prognosis observed in other elderly patients with COVID-19 and specific comorbidities. Furthermore, the data highlight the crucial role of monoclonal antibodies in reducing mortality among these vulnerable individuals.

Conflict of Interest

This manuscript was written as part of our routine work. Authors declare no conflict of interest regarding the submitted work.

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Ethical Approval statement

EPICOVIDEHA (www.clinicaltrials.gov; NCT04733729) is an international open web-based registry for patients with HM infected with SARS-CoV-2. This registry was centrally approved by the local ethics committee of the Fondazione Policlinico Universitario Agostino Gemelli—IRCCS, Università Cattolica del Sacro Cuore of Rome, Italy (Study ID: 3226). Additionally, if applicable, the respective local ethics committee of each participating institution might have approved the EPICOVIDEHA.

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Age, Successive Waves, Immunization, and Mortality in Elderly COVID-19 Haematological Patients: EPICOVIDEHA Findings

Table 1 . Demographic and clinical characteristics of the whole series of older hematologic patients with COVID-19 and of the four groups of different age.

	Overall		**65-70 years old**		**71-75 years old**		**76-80 years old**		**>80 years old**		**p value**
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Sex											
Female	1510	41.9%	432	41.4%	344	36.9%	345	42.7%	389	47.5%	**<0.001**
Male	2093	58.1%	612	58.6%	588	63.1%	463	57.3%	430	52.5%	
Age	74 (70-80) [65-97]		68 (66-69) [65-70]		73 (72-74) [71-75]		78 (77-79) [76-80]		84 (82-87) [81-97]		
<71 years old	1044	29.0%	1044	100.0%	0	0.0%	0	0.0%	0	0.0%	
71-75 years old	932	25.9%	0	0.0%	932	100.0%	0	0.0%	0	0.0%	
76-80 years old	808	22.4%	0	0.0%	0	0.0%	808	100.0%	0	0.0%	
>80 years old	819	22.7%	0	0.0%	0	0.0%	0	0.0%	819	100.0%	
Comorbidities											
No comorbidities	909	25.2%	319	30.6%	247	26.5%	179	22.2%	164	20.0%	
1 comorbidity	1241	34.4%	355	34.0%	327	35.1%	296	36.6%	263	32.1%	**<0.001**
2 comorbidities	834	23.1%	242	23.2%	195	20.9%	191	23.6%	206	25.2%	
3 or more comorbidities	619	17.2%	128	12.3%	163	17.5%	142	17.6%	186	22.7%	
Chronic cardiopathy	1826	50.7%	419	40.1%	436	46.8%	449	55.6%	522	63.7%	**0.001**
Chronic pulmonary disease	654	18.2%	150	14.4%	171	18.3%	143	17.7%	190	23.2%	**<0.001**
Diabetes mellitus	706	19.6%	168	16.1%	197	21.1%	189	23.4%	152	18.6%	**<0.001**
Liver disease	156	4.3%	49	4.7%	45	4.8%	34	4.2%	28	3.4%	0.465
Obesity	244	6.8%	89	8.5%	69	7.4%	50	6.2%	36	4.4%	**0.004**
Renal impairment	388	10.8%	80	7.7%	92	9.9%	85	10.5%	131	16.0%	**<0.001**

	Overall		65-70 years old		71-75 years old		76-80 years old		>80 years old		p value
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Smoking history	453	12.6%	157	15.0%	122	13.1%	97	12.0%	77	9.4%	**0.003**
No risk factor identified	900	25.0%	316	30.3%	246	26.4%	176	21.8%	162	19.8%	**<0.001**
Hematological maligancies											
Leukemia	1456	40.4%	405	38.8%	342	36.7%	325	40.2%	384	46.9%	
Acute lymphoid leukemia	47	1.3%	22	2.1%	8	0.9%	11	1.4%	6	0.7%	
Chronic lymphoid leukemia	616	17.1%	154	14.8%	166	17.8%	146	18.1%	150	18.3%	
Acute myeloid leukemia	328	9.1%	127	12.2%	76	8.2%	64	7.9%	61	7.4%	
Chronic myeloid leukemia	95	2.6%	27	2.6%	27	2.9%	17	2.1%	24	2.9%	
Myelodisplastic syndrome	353	9.8%	68	6.5%	63	6.8%	80	9.9%	142	17.3%	
Hairy cell leukemia	17	0.5%	7	0.7%	2	0.2%	7	0.9%	1	0.1%	
Lymphoma	1128	31.3%	346	33.1%	318	34.1%	249	30.8%	215	26.3%	
Hodgkin lymphoma	45	1.2%	23	2.2%	10	1.1%	9	1.1%	3	0.4%	
Non-Hodgkin lymphoma	1083	30.1%	323	30.9%	308	33.0%	240	29.7%	212	25.9%	
PH negative myeloproliferative diseases	264	7.3%	69	6.6%	72	7.7%	58	7.2%	65	7.9%	**0.001**
Essential thrombocythemia	65	1.8%	8	0.8%	16	1.7%	19	2.4%	22	2.7%	
Myelofibrosis	126	3.5%	41	3.9%	36	3.9%	22	2.7%	27	3.3%	
Polycythemia vera	66	1.8%	16	1.5%	19	2.0%	16	2.0%	15	1.8%	
Systemic mastocytosis	7	0.2%	4	0.4%	1	0.1%	1	0.1%	1	0.1%	
Plasma cell disorders	740	20.5%	219	21.0%	197	21.1%	174	21.5%	150	18.3%	
Multiple myeloma	725	20.1%	215	20.6%	190	20.4%	171	21.2%	149	18.2%	
Amyloid light-chain amyloidosis	15	0.4%	4	0.4%	7	0.8%	3	0.4%	1	0.1%	
Other hematological malignancies	15	0.4%	5	0.5%	3	0.3%	2	0.2%	5	0.6%	
Aplastic anemia	15	0.4%	5	0.5%	3	0.3%	2	0.2%	5	0.6%	
Last haematological treatment before COVID-19											
No treatment	574	15.9%	138	13.2%	138	14.8%	117	14.5%	181	22.1%	
alloHSCT	53	1.5%	41	3.9%	12	1.3%	0	0.0%	0	0.0%	
autoHSCT	34	0.9%	26	2.5%	8	0.9%	0	0.0%	0	0.0%	
CAR-T	16	0.4%	10	1.0%	4	0.4%	2	0.2%	0	0.0%	
Conventional chemotherapy	512	14.2%	173	16.6%	112	12.0%	111	13.7%	116	14.2%	**0.001**
Demethylating agents	246	6.8%	52	5.0%	65	7.0%	62	7.7%	67	8.2%	
Immuno-chemotherapy	987	27.4%	295	28.3%	291	31.2%	233	28.8%	168	20.5%	
Immunotherapy	197	5.5%	60	5.7%	42	4.5%	51	6.3%	44	5.4%	
Supportive/Palliative	149	4.1%	23	2.2%	30	3.2%	35	4.3%	61	7.4%	
Targeted therapy	835	23.2%	226	21.6%	230	24.7%	197	24.4%	182	22.2%	
Status malignancy before COVID-19											
Controlled disease	1462	40.6%	485	46.5%	380	40.8%	337	41.7%	260	31.7%	
Stable disease	839	23.3%	186	17.8%	212	22.7%	186	23.0%	255	31.1%	**<0.001**
Active disease	1186	32.9%	334	32.0%	307	32.9%	266	32.9%	279	34.1%	
Unknown	116	3.2%	39	3.7%	33	3.5%	19	2.4%	25	3.1%	
Neutrophils at COVID-19 onset											
<501	256	7.1%	93	8.9%	63	6.8%	56	6.9%	44	5.4%	**0.017**

	Overall		65-70 years old		71-75 years old		76-80 years old		>80 years old		p value
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
501 - 999	191	5.3%	64	6.1%	50	5.4%	37	4.6%	40	4.9%	
>999	2665	74.0%	726	69.5%	678	72.7%	613	75.9%	648	79.1%	
Lymphocytes at COVID-19 onset											
<201	334	9.3%	125	12.0%	82	8.8%	72	8.9%	55	6.7%	
201 - 499	538	14.9%	149	14.3%	137	14.7%	133	16.5%	119	14.5%	**0.001**
>499	2265	62.9%	615	58.9%	589	63.2%	502	62.1%	559	68.3%	
Vaccine doses before COVID-19											
Not vaccinated	2468	68.5%	721	69.1%	629	67.5%	541	67.0%	577	70.5%	
One dose	81	2.2%	29	2.8%	23	2.5%	16	2.0%	13	1.6%	
Two doses	442	12.3%	135	12.9%	115	12.3%	107	13.2%	85	10.4%	0.172
Three doses	570	15.8%	148	14.2%	148	15.9%	139	17.2%	135	16.5%	
Four doses	42	1.2%	11	1.1%	17	1.8%	5	0.6%	9	1.1%	
Last vaccination before COVID-19											
mRNA	1025	28.4%	272	26.1%	278	29.8%	242	30.0%	233	28.4%	
Vector-based	66	1.8%	35	3.4%	15	1.6%	13	1.6%	3	0.4%	**<0.001**
Inactivated	40	1.1%	16	1.5%	8	0.9%	10	1.2%	6	0.7%	
Time of COVID-19 diagnosis											
1st wave January-April 2020	820	22.8%	192	18.4%	192	20.6%	183	22.6%	253	30.9%	
1st interwaves	185	5.1%	66	6.3%	50	5.4%	31	3.8%	38	4.6%	
2nd wave September 2020-March 2021	1198	33.3%	384	36.8%	316	33.9%	269	33.3%	229	28.0%	
2nd interwaves	230	6.4%	70	6.7%	52	5.6%	60	7.4%	48	5.9%	**<0.001**
3rd wave September 2021-March 2022	1055	29.3%	298	28.5%	292	31.3%	245	30.3%	220	26.9%	
3rd interwaves	68	1.9%	19	1.8%	20	2.1%	10	1.2%	19	2.3%	
4th wave May-July 2022	47	1.3%	15	1.4%	10	1.1%	10	1.2%	12	1.5%	
SARS-CoV-2 variant											
Wild type	113	3.1%	37	3.5%	31	3.3%	27	3.3%	18	2.2%	
Alpha	45	1.2%	13	1.2%	8	0.9%	13	1.6%	11	1.3%	
Delta	111	3.1%	32	3.1%	32	3.4%	31	3.8%	16	2.0%	**0.001**
Omicron	437	12.1%	120	11.5%	115	12.3%	104	12.9%	98	12.0%	
Not tested	2897	80.4%	842	80.7%	746	80.0%	633	78.3%	676	82.5%	
COVID-19 severity											
Asymptomatic	557	15.5%	187	17.9%	144	15.5%	116	14.4%	110	13.4%	
Mild infection	937	26.0%	276	26.4%	227	24.4%	210	26.0%	224	27.4%	**<0.001**
Severe infection	1554	43.1%	377	36.1%	389	41.7%	369	45.7%	419	51.2%	
Critical infection	555	15.4%	204	19.5%	172	18.5%	113	14.0%	66	8.1%	
COVID-19 symptoms at onset											
Pulmonary	1429	39.7%	379	36.3%	369	39.6%	327	40.5%	354	43.2%	
Pulmonary + extrapulmonary	912	25.3%	250	23.9%	235	25.2%	210	26.0%	217	26.5%	**0.010**
Extrapulmonary	605	16.8%	195	18.7%	152	16.3%	129	16.0%	129	15.8%	
Screening	657	18.2%	220	21.1%	176	18.9%	142	17.6%	119	14.5%	
Stay during COVID-19 episode											

	Overall		65-70 years old		71-75 years old		76-80 years old		>80 years old		p value
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Home	965	26.8%	309	29.6%	251	26.9%	217	26.9%	188	23.0%	**0.016**
Hospital	2638	73.2%	735	70.4%	681	73.1%	591	73.1%	631	77.0%	
Duration of the stay in hospital	14 (7-23) [1-190]		15 (8-27) [1-155]		14 (8-23) [1-179]		14 (7-23) [1-190]		12 (7-20) [1-135]		
ICU stay	560	21.2%	205	27.9%	174	25.6%	115	19.5%	66	10.5%	**<0.001**
Duration of the ICU stay	10 (5-18) [1-115]		11 (6-20) [1-74]		10 (5-16) [1-80]		9 (4-15) [1-115]		7 (3-14) [1-68]		
COVID-19 treatment											
No specific treatment reported	752	20.9%	201	19.3%	204	21.9%	157	19.4%	190	23.2%	
Antivirals +/- corticosteroids +/- plasma	332	9.2%	97	9.3%	104	11.2%	67	8.3%	64	7.8%	
Antivirals + monoclonal antibodies +/- corticosteroids +/- plasma	106	2.9%	34	3.3%	34	3.6%	23	2.8%	15	1.8%	
Monoclonal antibodies +/- corticosteroids +/- plasma	255	7.1%	89	8.5%	64	6.9%	64	7.9%	38	4.6%	**0.002**
Plasma +/- corticosteroids	34	0.9%	11	1.1%	10	1.1%	9	1.1%	4	0.5%	
Corticosteroids	385	10.7%	94	9.0%	88	9.4%	97	12.0%	106	12.9%	
Unknown	1739	48.3%	518	49.6%	428	45.9%	391	48.4%	402	49.1%	

Table 2. Outcome of the whole series of older hematologic patients with COVID-19 and of the four groups of different age.

	Overall		**65-70 years old**		**71-75 years old**		**76-80 years old**		**>80 years old**		**p value**
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Follow up time	39 (14-133.5) [0-792]		50 (19-152) [0-792]		45 (17-139) [0-733]		35 (13-121) [0-760]		27 (10-103) [0-627]		**<0.001**
Follow up time, alive	75.5 (26-191) [0-792]		82 (29-199) [0-792]		81 (27-206) [0-733]		69 (23-174.5) [0-760]		63 (23-191) [0-627]		0.099
Follow up time, dead	15 (7-33) [0-657]		19 (10-37) [0-528]		16 (10-38) [0-657]		15 (7-30) [0-577]		12 (5-27) [0-584]		**<0.001**
Overall											**<0.001**
Mortality	1107	30.7%	252	24.1%	258	27.7%	261	32.3%	336	41.0%	
Reason for death											
COVID-19	753	20.9%	164	15.7%	176	18.9%	184	22.8%	229	28.0%	
COVID-19 + hematological malignancy	264	23.8%	66	6.3%	57	6.1%	59	7.3%	82	10.0%	
Hematological maligancies +/- other reasons	90	2.5%	22	2.1%	25	2.7%	18	2.2%	25	3.1%	
Day 30											**<0.001**
Mortality	852	23.6%	175	16.8%	194	20.8%	209	25.9%	274	33.5%	
Reason for death											
COVID-19	598	16.6%	113	10.8%	138	14.8%	151	18.7%	196	23.9%	
COVID-19 + hematological malignancy	208	5.8%	49	4.7%	44	4.7%	47	5.8%	68	8.3%	
Hematological maligancies +/- other reasons	46	1.3%	13	1.2%	12	1.3%	11	1.4%	10	1.2%	
Day 90											**<0.001**
Mortality	1038	28.8%	229	21.9%	244	26.2%	251	31.1%	314	38.3%	
Reason for death											
COVID-19	723	20.1%	152	14.6%	171	18.3%	179	22.2%	221	27.0%	
COVID-19 + hematological malignancy	252	7.0%	61	5.8%	55	5.9%	57	7.1%	79	9.6%	
Hematological maligancies +/- other reasons	63	1.7%	16	1.5%	18	1.9%	15	1.9%	14	1.7%	
Day 365											**<0.001**
Mortality	1095	30.4%	249	23.9%	256	27.5%	260	32.2%	330	40.3%	
Reason for death											
COVID-19	745	20.7%	162	15.5%	175	18.8%	183	22.6%	225	27.5%	
COVID-19 + hematological malignancy	262	7.3%	65	6.2%	57	6.1%	59	7.3%	81	9.9%	
Hematological maligancies +/- other reasons	88	2.4%	22	2.1%	24	2.6%	18	2.2%	24	2.9%	

Table 3. Univariable and multivariable regression analysis on the effect of different parameters on 90-day mortality.

	UNIVARIABLE				MULTIVARIABLE			
	p value	HR	95% C.I.		p value	HR	95% C.I.	
			Lower	Upper			Lower	Upper
Age								
65-70 years old	-	-	-	-	-	-	-	-
71-75 years old	**0.011**	1.258	1.054	1.502	**0.005**	1.308	1.082	1.582
76-80 years old	**<.001**	1.584	1.327	1.889	**<.001**	1.706	1.411	2.063
>80 years old	**<.001**	2.119	1.792	2.506	**<.001**	2.542	2.107	3.067
Sex	0.137	1.097	0.971	1.239				
Comorbidities								
No comorbidities	-	-	-	-				
1 comorbidity	**0.024**	1.216	1.027	1.441				
2 comorbidities	**<.001**	1.440	1.206	1.720				
3 or more comorbidities	**<.001**	1.793	1.494	2.152				
Chronic cardiopathy	**<.001**	1.382	1.225	1.559	**<.001**	1.262	1.107	1.438
Chronic pulmonary disease	**<.001**	1.277	1.106	1.475	0.832	0.983	0.839	1.152
Diabetes	**0.024**	1.179	1.022	1.362	0.417	1.067	0.913	1.246
Liver disease	**0.003**	1.484	1.149	1.918	**<.001**	1.573	1.204	2.054
Obesity	0.175	1.166	0.934	1.455				
Renal impairment	**<.001**	1.645	1.392	1.943	**0.023**	1.233	1.029	1.476
Smoking history	0.083	1.162	0.981	1.376	0.078	1.177	0.982	1.411
Neutrophils								
<501	-	-	-	-	-	-	-	-
501 - 999	0.312	0.859	0.639	1.154	0.890	1.022	0.756	1.381
>999	**<.001**	0.643	0.526	0.785	0.157	0.846	0.671	1.067
Lymphocytes								
< 201	**-**	-	-	-	-	-	-	-
201 - 499	**0.013**	0.766	0.620	0.946	**0.019**	0.769	0.618	0.958
>499	**<.001**	0.582	0.487	0.694	**<.001**	0.605	0.501	0.731
Type of cancer								
Acute leukaemia	**-**	-	-	-	**-**	-	-	-
Chronic myeloproliferative neoplasms (MPN)	**<.001**	0.494	0.378	0.645	**<.001**	0.586	0.436	0.787
CLL	**<.001**	0.633	0.510	0.786	**<.001**	0.632	0.495	0.807
Lymphoma	**<.001**	0.684	0.565	0.828	**<.001**	0.665	0.539	0.822
MDS	**0.030**	0.765	0.600	0.975	**0.015**	0.714	0.545	0.937
MM	**<.001**	0.595	0.481	0.735	**<.001**	0.607	0.481	0.765
Other	0.141	0.424	0.135	1.329	0.361	0.579	0.179	1.871
Status malignancies								
Controlled disease	-	-	-	-	-	-	-	-

	UNIVARIABLE				MULTIVARIABLE			
	p value	HR	95% C.I.		p value	HR	95% C.I.	
			Lower	Upper			Lower	Upper
Stable disease	0.847	1.017	0.854	1.212	0.794	1.027	0.843	1.251
Active disease	**<.001**	1.927	1.678	2.212	**<.001**	1.651	1.421	1.918
Unknown	**<.001**	2.520	1.887	3.367	**<.001**	1.860	1.370	2.526
Time last malignancy treatment before COVID-19								
Chemotherapy - In the last month	-	-	-	-				
Chemotherapy - In the last 3 months	0.798	1.026	0.843	1.250				
Chemotherapy - > 3 months	0.134	0.872	0.729	1.043				
HSCT/CAR-T - In the last 6 months	0.663	1.110	0.695	1.774				
HSCT/CAR-T - > 6 months	0.053	0.540	0.289	1.008				
No treatment - Not applicable	**0.031**	0.824	0.691	0.982				
Not reported	0.077	0.676	0.437	1.044				
Vaccine doses								
Not vaccinated	-	-	-	-	-	-	-	-
One dose	0.071	0.658	0.418	1.037	0.785	0.932	0.561	1.548
Two doses	**<.001**	0.644	0.519	0.799	0.684	0.947	0.727	1.233
Three doses	**<.001**	0.439	0.347	0.555	**0.009**	0.683	0.513	0.910
Four doses	**0.002**	0.172	0.055	0.535	0.079	0.354	0.111	1.127
Variant								
Wild type	-	-	-	-	-	-	-	-
Alpha	0.994	0.998	0.558	1.785	0.699	0.880	0.459	1.687
Delta	0.577	0.873	0.543	1.406	0.069	1.645	0.962	2.812
Omicron	**0.004**	0.559	0.377	0.828	0.326	1.247	0.803	1.939
Not tested	0.864	0.972	0.706	1.340	0.220	1.232	0.883	1.719
Symptoms at COVID-19 onset								
Pulmonary	-	-	-	-	-	-	-	-
Pulmonary + extrapulmonary	0.304	0.928	0.805	1.070	0.358	0.931	0.799	1.084
Extrapulmonary	**<.001**	0.507	0.417	0.618	**<.001**	0.658	0.534	0.812
Screening	**<.001**	0.550	0.457	0.662	**<.001**	0.634	0.514	0.782
ICU admission	**<.001**	3.157	2.782	3.584	**<.001**	2.903	2.517	3.347
COVID-19 treatment								
No specific treatment reported	-	-	-	-	-	-	-	-
Antivirals +/- corticosteroids +/- plasma	**<.001**	1.968	1.508	2.569	0.345	1.152	0.859	1.544
Antivirals + monoclonal antibodies +/- corticosteroids +/- plasma	0.553	1.151	0.723	1.831	0.546	0.854	0.512	1.425
Monoclonal antibodies +/- corticosteroids +/- plasma	0.425	0.853	0.577	1.261	**0.018**	0.589	0.380	0.915
Plasma +/- corticosteroids	**<.001**	2.871	1.702	4.840	0.159	1.485	0.857	2.575
Corticosteroids	**<.001**	2.303	1.799	2.947	**0.012**	1.407	1.077	1.837

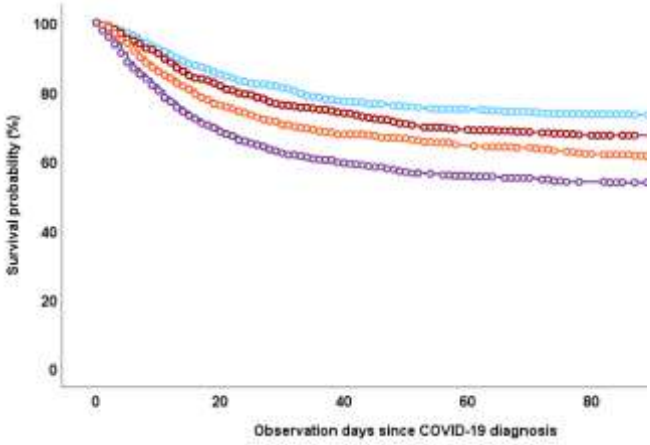
	UNIVARIABLE				MULTIVARIABLE			
	p value	HR	95% C.I.		p value	HR	95% C.I.	
			Lower	Upper			Lower	Upper
Unknown	**<.001**	2.215	1.819	2.697	**<.001**	1.486	1.181	1.869

Haematological malignancies, and COVID-19 in the elderly: how age, successive pandemic waves, and immunisation affect mortality: EPICOVIDEHA registry findings

Figures

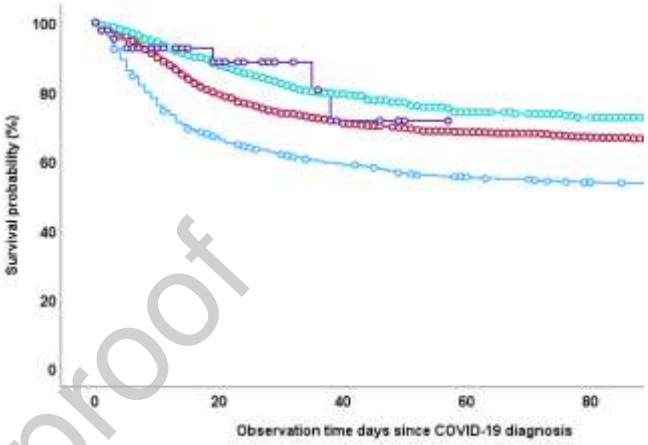
Figure 1. Survival probability by age group, diagnostic time and SARS-CoV-2 variant

A) Survival probability by age group



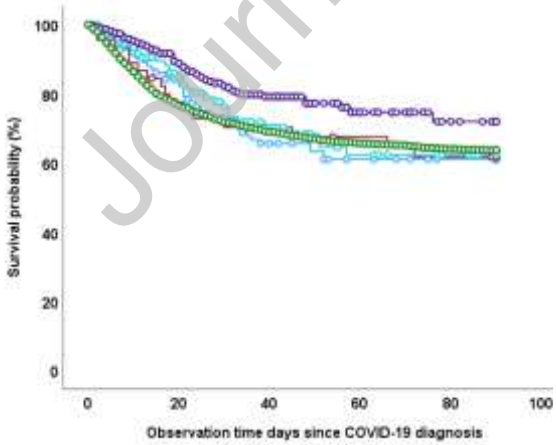
Overall comparison	p<0.001		
Pairwise comparisons	**65-70 years old**	**71-75 years old**	**76-80 years old**
71-75 years old	0.010		
76-80 years old	<.001	0.008	
>80 years old	<.001	<.001	<.001

B) Survival probability by diagnostic time



Overall comparison	p=0.001		
Pairwise comparisons	**1st wave**	**2nd wave**	**3rd wave**
2nd wave	0.781		
3rd wave	0.055	<0.001	
4th wave	0.458	0.412	0.818

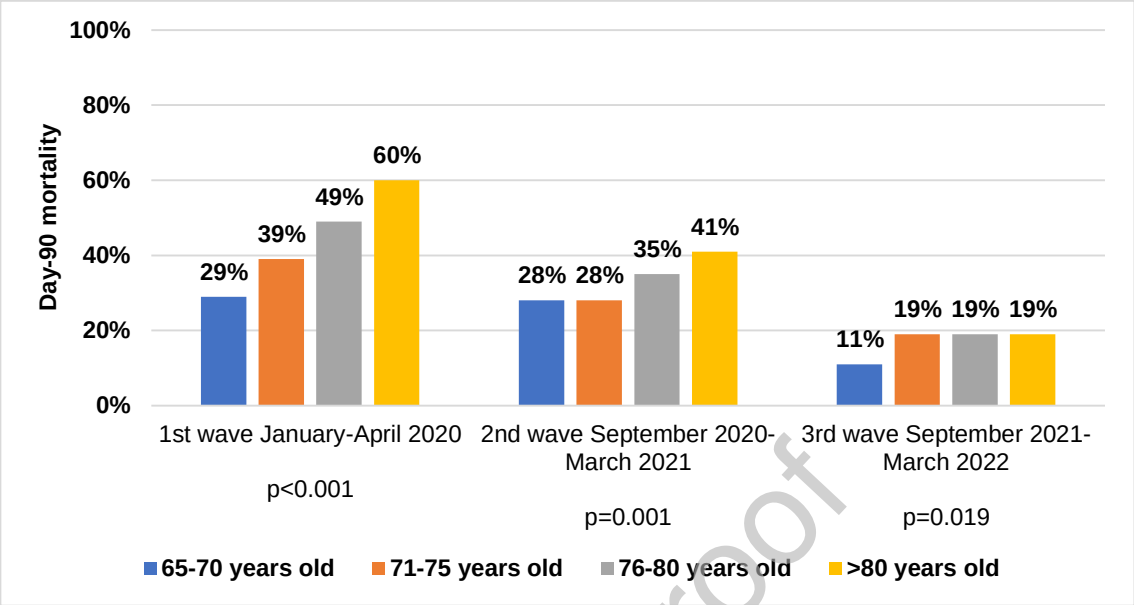
C) Survival probability by SARS-CoV-2 variant



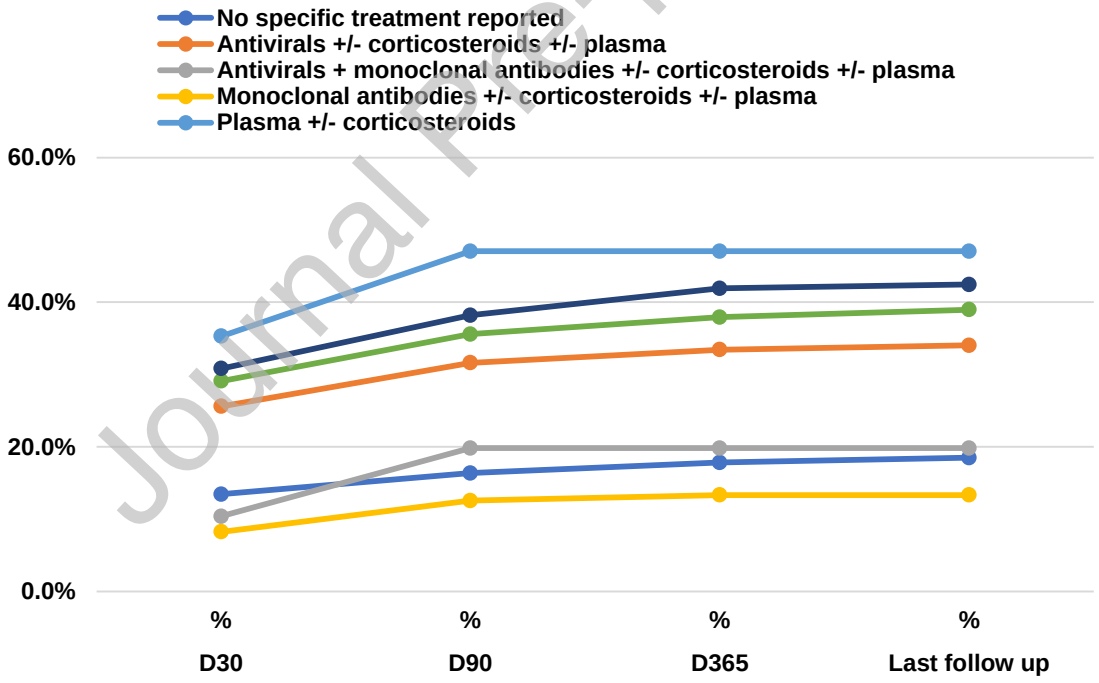
Overall comparison	p=0.001			
Pairwise comparisons	**Wild type**	**Alpha**	**Delta**	**Omicron**
Alpha	0.944			
Delta	0.650	0.778		
Omicron	0.010	0.096	0.071	
Not tested	0.967	0.900	0.456	0.001

Figure 2. Day 90 mortality rate by pandemic wave and COVID-19 treatment

A) Day 90 mortality rate by pandemic wave



B) Day 90 mortality rate by COVID-19 treatment



Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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