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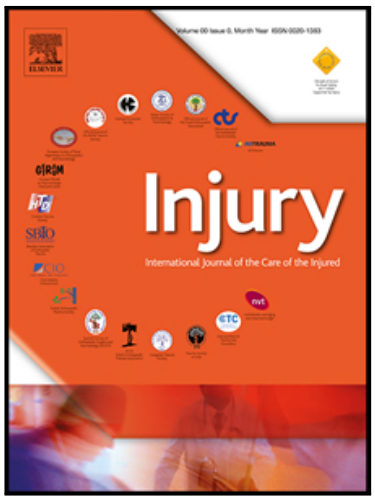

Health care utilization and outcomes in older adults after Traumatic Brain Injury: a CENTER-TBI study

Marjolein van der Vlegel , Ana Mikolić , Quentin Lee Hee , Z.L. Rana Kaplan , Isabel R.A. Retel Helmrich , Ernest van Veen , Nada Andelic , Nicole v. Steinbuechel , Anne Marie Plass , Marina Zeldovich , Lindsay Wilson , Andrew I.R. Maas , Juanita A. Haagsma , Suzanne Polinder , Cecilia Åkerlund , Pradeep George , Linda Lanyon , Visakh Muraleedharan , David Nelson , Krisztina Amrein , Erzsébet Ezer , Noémi Kovács , Béla Melegh , József Nyirádi , Viktória Tamás , Zoltán Vámos , Abayomi Sorinola , Nada Andelic , Lasse Andreassen , Audny Anke , Shirin Frisvold , Anna Antoni , Elisabeth Schwendenwein , Gérard Audibert , Philippe Azouvi , Maria Luisa Azzolini , Luigi Beretta , Maria Rosa Calvi , Ronald Bartels , Hugo den Boogert , Pál Barzó , Romuald Beauvais , Natascha Perera , Ronny Beer , Raimund Helbok , Bo-Michael Bellander , Antonio Belli , Habib Benali , Vincent Degos , Damien Galanaud , Vincent Perlbarg , Maurizio Berardino , Simona Cavallo , Morten Blaabjerg , Christina Rosenlund , Rico Frederik Schou , Peter Bragge , Alexandra Brazinova , Marek Majdan , Mark Steven Taylor , Veronika Zelinkova , Vibeke Brinck , Mike Jarrett , Joanne Brooker , Emma Donoghue , Anneliese Synnot , Camilla Brorsson , Lars-Owe Koskinen , Nina Sundström , Andras Buki , Endre Czeiter , Monika Bullinger , Manuel Cabeleira , Marek Czosnyka , Abhishek Dixit , Ari Ercole , Evgenios Koraropoulos , David Menon , Virginia Newcombe , Sophie Richter , Peter Smielewski , Emmanuel Stamatakis , Guy Williams , Stefan Winzeck , Frederick A. Zeiler , Alessio Caccioppola , Emiliana Calappi , Marco Carbonara , Fabrizio Ortolano , Tommaso Zoerle , Nino Stocchetti , Peter Cameron , Dashiell Gantner , Lynnette Murray , Tony Trapani , Shirley Vallance , Guillermo Carbayo Lozano , Inigo Pomposo , Ana M. Castaño-León , Pedro A. Gomez , Alfonso Lagares , Giorgio Chevallard , Arturo Chieregato , Giuseppe Citerio , Alessia Vargiolu , Iris Ceyisakar , Benjamin Gravesteijn , Juanita A. Haagsma , Jilske Huijben , Hester Lingsma , Daan Nieboer , Ana Mikolic , Suzanne Polinder , Charlie Sewalt , Ewout W. Steyerberg , Kimberley Velt , Daphne Voormolen , Eveline Wiegers , Wilco Peul , Jeroen T.J.M. van Dijck , Thomas A. van Essen , Roel P.J. van Wijk , Hans Clusmann , Mark Coburn , Ana Kowark , Rolf Rossaint , Jonathan Coles , Jamie D. Cooper , Marta Correia , Amra Čovid , Nicole von Steinbüchel , Nicola Curry , Simon Stanworth , Claire Dahyot-Fizelier , Paul Dark , Faye Johnson , Helen Dawes , Patrick Esser , Caroline van Heugten , Véronique De Keyser , Andrew I.R. Maas , Tomas Menovsky , Gregory Van der Steen , Francesco Della Corte , Francesca Grossi , Bart Depreitere ,

Đula Đilvesi , Jagoš Golubovic , Mladen Karan , Petar Vulekovic , Jens Dreier , Peter Vajkoczy , Stefan Wolf , Guy-Loup Dulière , Hugues Maréchal , Martin Fabricius , Daniel Kondziella , Valery L. Feigin , Kelly Jones , Braden Te Ao , Alice Theadom , Kelly Foks , Iain Haitsma , Victor Volovici , Alex Furmanov , Guy Rosenthal , Pablo Gagliardo , Guoyi Gao , Ji-yao Jiang , Alexandre Ghuysen , Lelde Giga , Egils Valeinis , Agate Ziverte , Ben Glocker , Daniel Rueckert , Johannes Gratz , Russell L. Gruen , Deepak Gupta , Cecilie Roe , Eirik Helseth , Olav Roise , Lindsay Horton , Lindsay Wilson , Peter J. Hutchinson , Angelos G. Kolias , Bram Jacobs , Joukje van der Naalt , Stefan Jankowski , Erwin Kompanje , Marjolein Timmers , Steven Laureys , Didier Ledoux , Benoit Misset , Fiona Lecky , Otesile Olubukola , Rolf Lefering , Nadine Schäfer , Valerie Legrand , Aurelie Lejeune , Emmanuel Vega , Julia Mattern , Leon Levi , Roger Lightfoot , Marc Maegele , Alex Manara , Matt Thomas , Geoffrey Manley , Costanza Martino , Oliver Sakowitz , Renan Sanchez-Porras , Alexander Younsi , Catherine McMahon , Ancuta Negru , Matej Oresic , Aarno Palotie , Paul M. Parizel , Jean-François Payen , Paolo Persona , Anna Piippo-Karjalainen , Matti Pirinen , Horia Ples , Jussi P. Posti , Louis Puybasset , Andreea Radoi , Arminas Ragauskas , Rahul Raj , Malinka Rambadagalla , Jonathan Rhodes , Sylvia Richardson , Samuli Ripatti , Saulius Rocka , Jonathan Rosand , Jeffrey V. Rosenfeld , Sandra Rossi , Martin Rusnák , Juan Sahuquillo , Janos Sandor , Silke Schmidt , Herbert Schoechl , Guus Schoonman , Toril Skandsen , Robert Stevens , William Stewart , Riikka Takala , Tomas Tamosuitis , Olli Tenovuo , Dick Tibboel , Christos Tolias , Cristina Maria Tudora , Mathieu van der Jagt , Wim Van Hecke , Dominique Van Praag , Thijs Vande Vyvere , Jan Verheyden , Paul M. Vespa , Anne Vik , Rimantas Vilcinis , Kevin K.W. Wang , Zhihui Yang , Peter Ylén

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Rico Frederik Schou , Peter Bragge , Alexandra Brazinova , Marek Majdan , Mark Steven Taylor , Veronika Zelinkova , Vibeke Brinck , Mike Jarrett , Joanne Brooker , Emma Donoghue , Anneliese Synnot , Camilla Brorsson , Lars-Owe Koskinen , Nina Sundström , Andras Buki , Endre Czeiter , Monika Bullinger , Manuel Cabeleira , Marek Czosnyka , Abhishek Dixit , Ari Ercole , Evgenios Koraropoulos , David Menon , Virginia Newcombe , Sophie Richter , Peter Smielewski , Emmanuel Stamatakis , Guy Williams , Stefan Winzeck , Frederick A. Zeiler , Alessio Caccioppola , Emiliana Calappi , Marco Carbonara , Fabrizio Ortolano , Tommaso Zoerle , Nino Stocchetti , Peter Cameron , Dashiell Gantner , Lynnette Murray , Tony Trapani , Shirley Vallance , Guillermo Carbayo Lozano , Inigo Pomposo , Ana M. Castaño-León , Pedro A. Gomez , Alfonso Lagares , Giorgio Chevallard , Arturo Chieregato , Giuseppe Citerio , Alessia Vargiolu , Iris Ceyisakar , Benjamin Gravesteijn , Juanita A. Haagsma , Jilske Huijben , Hester Lingsma , Daan Nieboer , Ana Mikolic , Suzanne Polinder , Charlie Sewalt , Ewout W. Steyerberg , Kimberley Velt , Daphne Voormolen , Eveline Wiegers , Wilco Peul , Jeroen T.J.M. van Dijck , Thomas A. van Essen , Roel P.J. van Wijk , Hans Clusmann , Mark Coburn , Ana Kowark , Rolf Rossaint , Jonathan Coles , Jamie D. Cooper , Marta Correia , Amra Čovid , Nicole von Steinbüchel , Nicola Curry , Simon Stanworth , Claire Dahyot-Fizelier , Paul Dark , Faye Johnson , Helen Dawes , Patrick Esser , Caroline van Heugten , Véronique De Keyser , Andrew I.R. Maas , Tomas Menovsky , Gregory Van der Steen , Francesco Della Corte , Francesca Grossi , Bart Depreitere , Đula Đilvesi , Jagoš Golubovic , Mladen Karan , Petar Vulekovic , Jens Dreier , Peter Vajkoczy , Stefan Wolf , Guy-Loup Dulière , Hugues Maréchal , Martin Fabricius , Daniel Kondziella , Valery L. Feigin , Kelly Jones , Braden Te Ao , Alice Theadom , Kelly Foks , Iain Haitsma , Victor Volovici , Alex Furmanov , Guy Rosenthal , Pablo Gagliardo , Guoyi Gao , Ji-yao Jiang , Alexandre Ghuysen , Lelde Giga , Egils Valeinis , Agate Ziverte , Ben Glocker , Daniel Rueckert , Johannes Gratz , Russell L. Gruen , Deepak Gupta , Cecilie Roe , Eirik Helseth , Olav Roise , Lindsay Horton , Lindsay Wilson , Peter J. Hutchinson , Angelos G. Kolias , Bram Jacobs , Joukje van der Naalt , Stefan Jankowski , Erwin Kompanje , Marjolein Timmers , Steven Laureys , Didier Ledoux , Benoit Misset , Fiona Lecky , Otesile Olubukola , Rolf Lefering , Nadine Schäfer , Valerie Legrand , Aurelie Lejeune , Emmanuel Vega , Julia Mattern , Leon Levi , Roger Lightfoot , Marc Maegele , Alex Manara , Matt Thomas , Geoffrey Manley , Costanza Martino , Oliver Sakowitz , Renan Sanchez-Porras , Alexander Younsi , Catherine McMahon , Ancuta Negru , Matej Oresic , Aarno Palotie , Paul M. Parizel , Jean-François Payen , Paolo Persona , Anna Piippo-Karjalainen , Matti Pirinen , Horia Ples , Jussi P. Posti , Louis Puybasset , Andreea Radoi , Arminas Ragauskas , Rahul Raj , Malinka Rambadagalla , Jonathan Rhodes , Sylvia Richardson , Samuli Ripatti , Saulius Rocka , Jonathan Rosand , Jeffrey V. Rosenfeld , Sandra Rossi , Martin Rusnák , Juan Sahuquillo , Janos Sandor , Silke Schmidt , Herbert Schoechl , Guus Schoonman , Toril Skandsen , Robert Stevens , William Stewart , Riikka Takala , Tomas Tamosuitis , Olli Tenovuo , Dick Tibboel , Christos Tolias , Cristina Maria Tudora , Mathieu van der Jagt , Wim Van Hecke , Dominique Van Praag , Thijs Vande Vyvere , Jan Verheyden , Paul M. Vespa , Anne Vik , Rimantas Vilcinis , Kevin K.W. Wang , Zhihui Yang , Peter Ylén , Health care utilization and outcomes in older adults after Traumatic Brain Injury: a CENTER-TBI study, *Injury* (2022), doi: https://doi.org/10.1016/j.injury.2022.05.009

Highlights

- In the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study about a half of older adults (≥65) were admitted to the intensive care unit
- Pre-injury systemic disease, pre-injury psychiatric conditions, and lower educational level are important predictors of poorer outcomes in older adults across different domains: global functioning, health related quality of life and mental health.
- In older adults, increased age is associated with poorer global functioning and physical health related quality of life, but not with mental health outcomes, when adjusted for other important factors.
- Older adults have a high mortality rate, however, there should not be pessimism about outcomes in older adults who survive: A substantial number of older patients recovers to pre-injury health or reports symptoms rates comparable to the general TBI population.

Health care utilization and outcomes in older adults after Traumatic Brain Injury: a CENTER-TBI study

Marjolein van der Vlegel[1,*]m.vandervlegel@erasmusmc.nl, Ana Mikolić[1], Quentin Lee Hee[1], Z.L. Rana Kaplan[1], Isabel R.A. Retel Helmrich[1], Ernest van Veen[1,2], Nada Andelic[3], Nicole v. Steinbuechel[4], Anne Marie Plass[4], Marina Zeldovich[4], Lindsay Wilson[5], Andrew I. R. Maas[6], Juanita A. Haagsma[1], Suzanne Polinder[1,†], Cecilia Åkerlund[7], Pradeep George[7], Linda Lanyon[7], Visakh Muraleedharan[7], David Nelson[7], Krisztina Amrein[8], Erzsébet Ezer[8], Noémi Kovács[8], Béla Melegh[8], József Nyirádi[8], Viktória Tamás[8], Zoltán Vámos[8], Abayomi Sorinola[8], Nada Andelic[9], Lasse Andreassen[10], Audny Anke[10], Shirin Frisvold[10], Anna Antoni[11], Elisabeth Schwendenwein[11], Gérard Audibert[12], Philippe Azouvi[13], Maria Luisa Azzolini[14], Luigi Beretta[14], Maria Rosa Calvi[14], Ronald Bartels[15], Hugo den Boogert[15], Pál Barzó[16], Romuald Beauvais[17], Natascha Perera[17], Ronny Beer[18], Raimund Helbok[18], Bo-Michael Bellander[19], Antonio Belli[20], Habib Benali[21], Vincent Degos[21], Damien Galanaud[21], Vincent Perlbarg[21], Maurizio Berardino[22], Simona Cavallo[22], Morten Blaabjerg[23], Christina Rosenlund[23], Rico Frederik Schou[23], Peter Bragge[24], Alexandra Brazinova[25], Marek Majdan[25], Mark Steven Taylor[25], Veronika Zelinkova[25], Vibeke Brinck[26], Mike Jarrett[26], Joanne Brooker[27], Emma Donoghue[27], Anneliese Synnot[27,28], Camilla Brorsson[29], Lars-Owe Koskinen[29], Nina Sundström[29], Andras Buki[30], Endre Czeiter[30], Monika Bullinger[31], Manuel Cabeleira[32], Marek Czosnyka[32], Abhishek Dixit[32], Ari Ercole[32], Evgenios Koraropoulos[32], David Menon[32], Virginia Newcombe[32], Sophie Richter[32], Peter Smielewski[32], Emmanuel Stamatakis[32], Guy Williams[32], Stefan Winzeck[32], Frederick A. Zeiler[32], Alessio Caccioppola[33], Emiliana Calappi[33], Marco Carbonara[33], Fabrizio Ortolano[33], Tommaso Zoerle[33], Nino Stocchetti[33,34], Peter Cameron[35], Dashiell Gantner[35], Lynnette Murray[35], Tony Trapani[35], Shirley Vallance[35], Guillermo Carbayo Lozano[36], Inigo Pomposo[36], Ana M. Castaño-León[37], Pedro A. Gomez[37], Alfonso Lagares[37], Giorgio Chevallard[38], Arturo Chieregato[38], Giuseppe Citerio[39,40], Alessia Vargiolu[40], Iris Ceyisakar[41], Benjamin Gravesteijn[41], Juanita A. Haagsma[41], Jilske Huijben[41], Hester Lingsma[41], Daan Nieboer[41], Ana Mikolic[41], Suzanne Polinder[41], Charlie Sewalt[41], Ewout W. Steyerberg[41,42], Kimberley Velt[41], Daphne Voormolen[41], Eveline Wiegers[41], Wilco Peul[42,43], Jeroen T.J.M. van Dijck[42,43], Thomas A. van Essen[42,43], Roel P.J. van Wijk[42,43], Hans Clusmann[44], Mark Coburn[45], Ana Kowark[45], Rolf Rossaint[45], Jonathan Coles[46], Jamie D. Cooper[47], Marta Correia[48], Amra Čovid[49], Nicole von Steinbüchel[49], Nicola Curry[50], Simon Stanworth[50], Claire Dahyot-Fizelier[51], Paul Dark[52], Faye Johnson[52], Helen Dawes[53], Patrick Esser[53], Caroline van Heugten[53], Véronique De Keyser[54], Andrew I.R. Maas[54], Tomas Menovsky[54], Gregory Van der Steen[54], Francesco Della Corte[55], Francesca Grossi[55], Bart Depreitere[56], Đula Đilvesi[57], Jagoš Golubovic[57], Mladen Karan[57], Petar Vulekovic[57], Jens

Dreier[58], Peter Vajkoczy[58], Stefan Wolf[58], Guy-Loup Dulière[59], Hugues Maréchal[59], Martin Fabricius[60], Daniel Kondziella[60], Valery L. Feigin[61], Kelly Jones[61], Braden Te Ao[61], Alice Theadom[61], Kelly Foks[62], Iain Haitsma[62], Victor Volovici[62], Alex Furmanov[63], Guy Rosenthal[63], Pablo Gagliardo[64], Guoyi Gao[65], Ji-yao Jiang[65], Alexandre Ghuysen[66], Lelde Giga[67], Egils Valeinis[67], Agate Ziverte[67], Ben Glocker[68], Daniel Rueckert[68], Johannes Gratz[69], Russell L. Gruen[69], Deepak Gupta[70], Cecilie Roe[9], Eirik Helseth[71], Olav Roise[71], Lindsay Horton[72], Lindsay Wilson[72], Peter J. Hutchinson[73], Angelos G. Kolias[73], Bram Jacobs[74], Joukje van der Naalt[74], Stefan Jankowski[75], Erwin Kompanje[76], Marjolein Timmers[76], Steven Laureys[77], Didier Ledoux[77], Benoit Misset[77], Fiona Lecky[78,79], Otesile Olubukola[78], Rolf Lefering[80], Nadine Schäfer[80], Valerie Legrand[81], Aurelie Lejeune[82], Emmanuel Vega[82], Julia Mattern[89], Leon Levi[83], Roger Lightfoot[84], Marc Maegele[85], Alex Manara[86], Matt Thomas[86], Geoffrey Manley[87], Costanza Martino[88], Oliver Sakowitz[89,90], Renan Sanchez-Porras[90], Alexander Younsi[91], Catherine McMahon[92], Ancuta Negru[93], Matej Oresic[94], Aarno Palotie[95,96,97], Paul M. Parizel[98], Jean-François Payen[98], Paolo Persona[99], Anna Piippo-Karjalainen[100], Matti Pirinen[95], Horia Ples[93], Jussi P. Posti[101], Louis Puybasset[102], Andreea Radoi[103], Arminas Ragauskas[104], Rahul Raj[100], Malinka Rambadagalla[105], Jonathan Rhodes[106], Sylvia Richardson[107], Samuli Ripatti[95], Saulius Rocka[104], Jonathan Rosand[108], Jeffrey V. Rosenfeld[109], Sandra Rossi[99], Martin Rusnák[110], Juan Sahuquillo[103], Janos Sandor[111], Silke Schmidt[112], Herbert Schoechl[113], Guus Schoonman[114], Toril Skandsen[115], Robert Stevens[116], William Stewart[117], Riikka Takala[101], Tomas Tamosuitis[118], Olli Tenovuo[101], Dick Tibboel[119], Christos Tolias[120], Cristina Maria Tudora[93], Mathieu van der Jagt[121], Wim Van Hecke[122], Dominique Van Praag[123], Thijs Vande Vyvere[122], Jan Verheyden[122], Paul M. Vespa[124], Anne Vik[115], Rimantas Vilcinis[118], Kevin K.W. Wang[125], Zhihui Yang[125], Peter Ylén[126]

[1]Department of Public Health, Erasmus MC, Rotterdam, The Netherlands

[2]Department of Intensive Care Adults, Rotterdam, the Netherlands

[3]Department of Physical Medicine and Rehabilitation, Oslo University Hospital and University of Oslo, 0424 Oslo, Norway

[4]Institute of Medical Psychology and Medical Sociology, University Medical Center Göttingen (UMG)/ Georg-August-University, Göttingen, Germany

[5]Division of Psychology, University of Stirling, Stirling, UK

[6]Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium

[7]Karolinska Institutet, Stockholm, Sweden

[8]University of Pécs, Pécs, Hungary

[9]Oslo University Hospital and University of Oslo, Oslo, Norway

[10]University Hospital Northern Norway, Tromso, Norway;

[11]Medical University Vienna, Vienna, Austria;

[12]University Hospital Nancy, Nancy, France

[13]Raymond Poincare Hospital, Assistance Publique – Hopitaux de Paris, Paris, France;

[14]S. Raffaele University Hospital, Milan, Italy

[15]Radboud University Medical Center, Nijmegen, The Netherlands

[16]University of Szeged, Szeged, Hungary

[17]ARTTIC, Munchen, Germany

[18]Medical University of Innsbruck, Innsbruck, Austria

[19]Karolinska University Hospital, Stockholm, Sweden

[20]NIHR Surgical Reconstruction and Microbiology Research Centre, Birmingham, UK

[21]Assistance Publique – Hopitaux de Paris, Paris, France

[22]AOU Città della Salute e della Scienza di Torino - Orthopedic and Trauma Center, Torino, Italy

[23]Odense University Hospital, Odense, Denmark

[24]Monash University, Victoria, Australia

[25]Trnava University, Trnava, Slovakia

[26]Quesgen Systems Inc., Burlingame, California, USA

[27]Monash University, Melbourne, Australia

[28]La Trobe University, Melbourne, Australia

[29]Umeå University, Umeå, Sweden

[30]University of Pécs, Hungary

[31]Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

[32]University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

[33]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Italy

[34]Milan University

[35]Monash University, Melbourne, Victoria, Australia

[36]Hospital of Cruces, Bilbao, Spain

[37]Hospital Universitario 12 de Octubre, Madrid, Spain

[38]Niguarda Hospital, Milan, Italy

[39]Università Milano Bicocca, Milano, Italy

[40]ASST di Monza, Monza, Italy

[41]Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands

[42]Leiden University Medical Center, Leiden, The Netherlands

[43]Medical Center Haaglanden, The Hague, The Netherlands

[44]Aachen University, Aachen, Germany

[45]University Hospital of Aachen, Aachen, Germany

[46]Cambridge University Hospital NHS Foundation Trust, Cambridge, UK

[47]Monash University and The Alfred Hospital, Melbourne, Victoria, Australia

[48]MRC Cognition and Brain Sciences Unit, Cambridge, UK

[49]Universitätsmedizin Göttingen, Göttingen, Germany

[50]Oxford University Hospitals NHS Trust, Oxford, UK

[51]CHU Poitiers, Potiers, France

[52]Salford Royal Hospital NHS Foundation Trust, Salford, UK

[53]Oxford Brookes University, Oxford, UK

[54]Antwerp University Hospital and University of Antwerp, Edegem, Belgium

[55]Maggiore Della Carità Hospital, Novara, Italy

[56]University Hospitals Leuven, Leuven, Belgium

[57]University of Novi Sad, Novi Sad, Serbia

[58]Charité – Universitätsmedizin Berlin, Berlin, Germany

[59]CHR Citadelle, Liège, Belgium

[60]Region Hovedstaden Rigshospitalet, Copenhagen, Denmark

[61]Auckland University of Technology, Auckland, New Zealand

[62]Erasmus MC, Rotterdam, the Netherlands

[63]Hadassah-Hebrew University Medical Center, Jerusalem, Israel

[64]Fundación Instituto Valenciano de Neurorrehabilitación (FIVAN), Valencia, Spain

[65]Shanghai Renji Hospital, Shanghai Jiaotong University/School of Medicine, Shanghai, China;

[66]CHU, Liège, Belgium

[67]Pauls Stradins Clinical University Hospital, Riga, Latvia

[68]Imperial College London, London, UK

[69]Medical University of Vienna, Austria

[70]All India Institute of Medical Sciences, New Delhi, India

[71]Oslo University Hospital, Oslo, Norway

[72]University of Stirling, Stirling, UK

[73]Addenbrooke's Hospital and University of Cambridge, Cambridge, UK

[74]University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[75]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

[76]Erasmus Medical Center, Rotterdam, The Netherlands

[77]University of Liège, Liège, Belgium

[78]University of Sheffield, Sheffield, UK

[79]Salford Royal Hospital, Salford UK

[80]Witten/Herdecke University, Cologne, Germany

[81]ICON, Paris, France

[82]Lille University Hospital, Lille, France

[83]Rambam Medical Center, Haifa, Israel

[84]University Hospitals Southhampton NHS Trust, Southhampton, UK

[85]Cologne-Merheim Medical Center (CMMC), Witten/Herdecke University, Cologne, Germany

[86]Southmead Hospital, Bristol, Bristol, UK

[87]University of California, San Francisco, California, USA

[88]M. Bufalini Hospital, Cesena, Italy

[89]University Hospital Heidelberg, Heidelberg, Germany

[90]Klinik für Neurochirurgie, Klinikum Ludwigsburg, Ludwigsburg, Germany

[91]University of Manitoba, Winnipeg, MB, Canada

[92]The Walton Centre NHS Foundation Trust, Liverpool, UK

[93]Emergency County Hospital Timisoara, Timisoara, Romania

[94]Örebro University, Örebro, Sweden

[95]University of Helsinki, Helsinki, Finland

[96]Massachusetts General Hospital, Boston, MA, USA

[97]The Broad Institute of MIT and Harvard, Cambridge, MA, USA

[98]University Hospital of Grenoble, Grenoble, France

[99]Azienda Ospedaliera Università di Padova, Padova, Italy

[100]Helsinki University Central Hospital

[101]Turku University Hospital and University of Turku, Turku, Finland

[102]Pitié -Salpêtrière Teaching Hospital, Assistance Publique, Hôpitaux de Paris and University Pierre et Marie Curie, Paris, France

[103]Vall d'Hebron Research Institute, Barcelona, Spain

[104]Kaunas University of Technology and Vilnius University, Vilnius, Lithuania

[105]Rezekne Hospital, Latvia

[106]NHS Lothian and University of Edinburg, Edinburgh, UK

[107]Cambridge Institute of Public Health, Cambridge, UK

[108]The Broad Institute, Cambridge MA Harvard Medical School and Massachusetts General Hospital, Boston MA, USA

[109]The Alfred Hospital, Monash University, Melbourne, Victoria, Australia

[110]International Neurotrauma Research Organisation, Vienna, Austria

[111]University of Debrecen, Debrecen, Hungary

[112]University Greifswald, Greifswald, Germany

[113]AUVA Trauma Hospital, Salzburg, Austria

[114]Elisabeth-Twee Steden Ziekenhuis, Tilburg, The Netherlands

[115]Norwegian University of Science and Technology, NTNU and St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

[116]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[117]Queen Elizabeth University Hospital and University of Glasgow, Glasgow, UK

[118]Kaunas University of Health Sciences, Kaunas, Lithuania,

[119]Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands

[120]Kings College London, London, UK

[121]Erasmus MC – University Medical Center Rotterdam, Rotterdam, The Netherlands

[122]icoMetrix NV, Leuven, Belgium

[123]Antwerp University Hospital, Edegem, Belgium

[124]University of California, Los Angeles, California, USA

[125]University of Florida, Gainesville, Florida, USA

[126]VTT Technical Research Centre, Tampere, Finland

[*]**Corresponding author**: Marjolein van der Vlegel; Erasmus MC University Medical Center Rotterdam, Department of Public Health, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands

[†]the CENTER-TBI Participants and Investigators

Abstract

Introduction: The incidence of traumatic brain injury (TBI) is increasingly common in older adults aged ≥65 years, forming a growing public health problem. However, older adults are underrepresented in TBI research. Therefore, we aimed to provide an overview of health-care utilization, and of six-month outcomes after TBI and their determinants in older adults who sustained a TBI.

Methods: We used data from the prospective multi-center Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. In-hospital and post-hospital health care utilization and outcomes were described for patients aged ≥65 years. Ordinal and linear regression analyses were performed to identify determinants of the Glasgow Outcome Scale Extended (GOSE), health-related quality of life (HRQoL), and mental health symptoms six-months post-injury.

Results: Of 1254 older patients, 45% were admitted to an ICU with a mean length of stay of 9 days. Nearly 30% of the patients received inpatient rehabilitation. In total, 554/1254 older

patients completed the six-month follow-up questionnaires. The mortality rate was 9% after mild and 60% after moderate/severe TBI, and full recovery based on GOSE was reported for 44% of patients after mild and 6% after moderate/severe TBI. Higher age and increased injury severity were primarily associated with functional impairment, while pre-injury systemic disease, psychiatric conditions and lower educational level were associated with functional impairment, lower generic and disease-specific HRQoL and mental health symptoms.

Conclusion: The rate of impairment and disability following TBI in older adults is substantial, and poorer outcomes across domains are associated with worse preinjury health. Nonetheless, a considerable number of patients fully or partially returns to their preinjury functioning. There should not be pessimism about outcomes in older adults who survive.

Keywords

Traumatic brain injury, older adults, outcomes, health care utilization, health-related quality of life, mental health

Introduction

Traumatic brain injury (TBI) is a growing public health problem and a major cause of death and disability worldwide [1]. TBI can cause long-term impairment in physical, cognitive and emotional functioning [2-4]. In recent decades, there is a shift in the TBI population towards older age groups (≥65 years), especially in high-income countries where falls represent the primary cause of TBI [5]. This can be explained by a combination of improved traffic safety regulations, resulting in a decrease in road traffic injuries, and increased life expectancy with greater mobility in older people [5].

Compared to younger TBI patients, older patients have longer hospital stays [6, 7], a slower recovery [8-10] and are more likely to die due to their TBI. [11] Recovery after TBI in older adults may be hampered by the presence of comorbidity, the presence of physical and mental health problems prior to injury, and the use of medication, which could complicate the treatment of TBI. Prior studies suggest that measures of pre-injury functioning and frailty are stronger predictors of outcome than age [12]. Nevertheless, previous TBI studies have often excluded older adults, especially those with pre-existing psychiatric and neurological problems [13]. While results from younger adult studies suggest a strong relationship between pre-injury characteristics and outcome after TBI, evidence from older adult cohorts is needed [14]. Chronic health complaints are also associated with increased healthcare utilization and costs [15]. In the general injury population, older patients have a higher health care utilization after discharge [16, 17]. A prior study found that older patients (75-84 years) had significantly higher rates of

rehospitalisation, home visits and informal care, and significantly lower rates of out-patient rehabilitation care compared to younger patients (55-74 years) [18].

Research on both health-related quality of life (HRQoL) and psychological outcomes in older adults after TBI is scarce. Previous HRQoL studies included small sample sizes and few studies included both generic and disease-specific measures of HRQoL [19]. In some studies, individuals showed a higher risk for emergence of psychiatric disorders including depression, anxiety and post-traumatic stress disorder (PTSD) after TBI [20], whereas in other studies older adults reported less psychological distress and less symptoms of depression and anxiety than younger adults [14]. Nonetheless, a systematic review on psychiatric assessments after TBI, concluded that psychological outcomes were insufficiently addressed in the emerging group of older TBI patients [20].

Since the number of older adults with TBI is substantial and has been increasing, it is important to investigate characteristics and outcomes in the older TBI population [21]. A recent systematic review on outcomes following mild TBI in older adults suggested "cautious optimism" in terms of long-term functional recovery and psychological health [14]. Better understanding of health care utilization and health outcomes of older people after TBI might help clinicians to set treatment goals. Furthermore, insight into patient characteristics related to poor outcomes in older patients may support the development of prognostic models for the older TBI population. Therefore, the aims of this study were to: 1) describe health care utilization following TBI in older adults, 2) assess six-month functional outcome, generic and disease-specific HRQoL, PTSD, anxiety and depression symptoms following TBI in older adults, and 3) identify determinants of six-month outcomes in the older TBI population.

Methods

Study design and population

We analyzed data from the prospective multi-center longitudinal observational Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) core study (version 3.0; registered at clinicaltrials.gov NCT02210221) [22]. Patients from 63 centers were invited to participate in the study from December 2014 to December 2017. Data was collected for patients with a clinical diagnosis of TBI, an indication for computed tomography (CT), who presented to a hospital within 24 hours after injury. Patients with a severe pre-existing neurological disorder, which could confound outcome assessments, were excluded. In CENTER-TBI core study, data from 4509 participants were available for analysis. For an overview of baseline characteristics, all adult (≥16 years) patients were included in this study. In

all further analyses, only patients aged ≥65 years were included: 1254 patients recruited from 59 participating centres .

Informed consent was obtained according to local regulations and the Medical Ethics Committees approved the CENTER-TBI study in all participating centers (https://www.centertbi.eu/project/ethical-approval).

Measures

Demographics, pre-injury characteristics

Sociodemographic characteristics (including sex, age, living situation, education level), medical history and clinical and injury characteristics were assessed at the time of enrolment in the study. Age was categorized into three groups: 65 to 74 years, 75 to 84 years, and 85 years or older for descriptive analyses, and used as a continuous variable in regression analyses.

Living situation was categorized as living alone or not. Level of education was divided into primary school, secondary school, post-high school training and college/university. Pre-injury health status was assessed with the American Society of Anaesthesiologists - physical status classification system (ASA-PS) and categorized as healthy, mild systemic disease and severe systemic disease/threat to life. Medication use included anticoagulants/platelets aggregation inhibitor use and beta-blocker use. Pre-injury psychiatric conditions included depression, anxiety, sleep disorder, schizophrenia, substance abuse disorder and other.

Early computed tomography (CT) assessed the presence of intracranial traumatic abnormalities. TBI severity was rated using the Glasgow Coma Scale (GCS) [23]. TBI was considered mild in patients with GCS 13-15, moderate in patients with GCS 9-12, and severe in patients with GCS of 3-8. The injury severity score (ISS), which ranges from 0-75, indicates overall injury severity. It is calculated as the sum of square of the three highest values of the Abbreviated Injury Scale Score (AIS) from different body regions [24]. Injury mechanism was categorized as falls, road traffic incident, and other.

Health care utilization

Data on hospital admission, ICU admission, and inpatient and outpatient rehabilitation were collected. Length of stay at the ward and ICU were collected using several sources of CENTER-TBI forms. For rehabilitation, the transitions of care forms were consulted. In addition to collecting information on post-injury pathways of care from providers, information on inpatient and outpatient rehabilitation were reported by a patient or proxy in questionnaires assessed at six-month follow-up. Inpatient rehabilitation included admission to a general, geriatric, psychiatric or specialized TBI rehabilitation unit, or nursing home unit. Outpatient rehabilitation included physical therapy, occupational therapy, speech therapy, therapeutic recreation,

cognitive remediation, vocational services, psychological services, nursing services, comprehensive day treatment, peer mentoring, social work, independent living, and home health.

Functional outcome at six months

Functional outcome was assessed at 6 months with the Glasgow Outcome Scale Extended (GOSE). When performed outside the time window (5-8 months), it was imputed based on GOSE measurements at other time points using a multi-state model [25]. The GOSE has eight ordinal categories: dead (1); vegetative state (2); lower severe disability (3); upper severe disability (4); lower moderate disability (5); upper moderate disability (6); lower good recovery (7); and upper good recovery (8). In this study, the categories 'vegetative state' and 'lower severe disability' were combined, as these could not be differentiated for GOSE ratings based on postal questionnaires because patients in a vegetative state require specialized tests for responsiveness, and this cannot be assessed by a questionnaire [26].

We gave centres flexibility in outcome assessment to help maximize follow-up rates and to tailor approaches to patients. The GOSE was assessed by a postal questionnaire or a structured interview by a trained assessor (telephone or face to face). Answers to GOSE questionnaires could be given by patients alone, and if that was not possible by patients with the help of a relative/ caregiver, or by a relative/caregiver alone. The ratings from interviews and questionnaires showed good agreement [27]. Interviews and questionnaires were scored centrally, and when both had been carried out, the rating was based on the interview.

Generic and disease-specific HRQoL at six months

Generic HRQoL was assessed using the 12-item short form health survey (SF-12v2) [28]. The HRQoL is summarized as a mental (MCS) and a physical component score (PCS). If there was no available SF-12v2 score, the score was derived using SF-36v2 if available [25]. The raw PCS-12 and MCS-12 scores were transposed as norm-based t-scores with a mean of 50 and a standard deviation of 10. Scores <40 were classified as impaired HRQoL [29].

The six-item Quality of Life after Brain Injury Overall Scale (QOLIBRI-OS) is a disease specific instrument and provides a profile of HRQoL in domains affected by TBI [30]. The instrument assesses the overall satisfaction with different domains of life. The total score scale ranges from 0-100 and scores <52 were classified as impaired HRQoL [31].

The measures of HRQoL were completed by patients alone, and for a small subset of patients by a relative/caregiver/friend. [32]

Psychological symptoms at six months

Post-traumatic stress

PTSD symptoms were assessed with the PCL-5 [33]. The PCL-5 includes 20 items reflecting the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) diagnostic criteria of PTSD. Items are scored on a five-point Likert scale ranging from 0 (not at all) to 4 (extremely) and the sum of scores ranges from 0 to 80. A total score ≥33 was considered clinically relevant [34].

Depression

Depression symptoms were assessed with The Patient Health Questionnaire (PHQ-9) [35]. It contains nine items, which are scored on a four-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). The sum score ranges from 0-27. A score of 5-9 indicated mild depressive symptoms and a score of ≥10 indicate moderate to severe depressive symptoms.

Anxiety

Anxiety symptoms were assessed with the Generalized Anxiety Disorder questionnaire (GAD-7) [36], a seven-item instrument with a four-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). The sum score ranges from 0-21 with a score from 5 to 9 indicating mild and a score of ≥10 indicating moderate to severe anxiety symptoms.

The measures of psychological symptoms were completed by patients alone.

All questionnaires that were not available in local languages of participating centres were translated and linguistically validated [37]. The questionnaires were scored centrally.

Statistical Analysis

Descriptive statistics for baseline characteristics, health care utilization, and health outcomes were presented with percentages for categorical variables and median and inter quartile range (IQR) for continuous variables. Differences in baseline characteristics were compared between three types of responders: those that completed at least one questionnaire (SF-12v2, QOLIBRI-OS, PCL-5, PHQ-9, GAD-7) at six months post-injury; non-responders; and those who died within six months post TBI, making use of chi-square and Mann-Whitney U tests. Health care utilization was reported for all patients with available data. Health outcomes were reported separately by age group (65–74, 75–84 and ≥85 years of age). Differences by age group were tested using the Kruskal-Wallis test. The association of possible determinants with multiple outcomes following TBI was analyzed with univariable and multivariable ordinal and linear regression analyses, and quantified with odds ratios (ordinal regression) and regression coefficients (linear regression

For the regression analyses, missing baseline characteristics were imputed using Multivariate Imputation by Chained Equation (MICE) approach based on an imputation model including all baseline characteristics, auxiliary variables (years of education) and all six-month outcomes,

using the *mice* package in R [38]. For ordinal logistic regression, the model performance was assessed with the area under the receiver operating curve, which corresponds to the c statistic. The c statistic was used to quantify the ability of the model to discriminate between patients with different outcome levels . The c statistic ranges between 0.50 (no discrimination) and 1.0 (perfect discrimination). For linear regression, model performance was quantified with the adjusted coefficient of determination (R^2).

Analyses were performed in SPSS V.25 (statistical package for social sciences, Chicago, Illinois, USA) and R (version 4.0.4) (R foundational for statistical computing, Vienna, Austria) [39].

Results

Baseline characteristics

The study included 1254 older adults (59% male) with a median age of 74 (IQR: 69-80) (**Table 1**). There were 355 (28%) patients categorized as having moderate/severe TBI, and the median ISS was 16 (IQR: 9-25). Most patients had pre-injury systemic disease (77%) and 13% had a pre-injury psychiatric condition. Falls were the primary cause of TBI (67%). In total, 554 of 1254 (44%) patients completed at least one survey on outcome after injury at six-month (**Table 1**). The median ISS was twice as high for deceased patients (26, IQR 20-43) compared to responders (13, IQR 8-21) and non-responders (13, IQR 8-25). Of responders, 14% were classified as moderate/severe TBI patients, while 69% of deceased patients were classified as moderate/severe TBI patients.

Compared to younger adult (16-64) patients, older patients were more often female, more often lived alone, reported more pre-injury psychical and psychiatric conditions and more often used anticoagulant, platelet aggregation inhibitors and beta-blockers (Table 1). The mortality at discharge was 19% in the older age group, compared to 6% in the younger population.

Health care utilization of older patients after TBI

Of 1254 patients, 84% (1046) were admitted to a hospital ward and/or ICU. (**Table 2)**. There were 566 (45%) patients admitted to an ICU with mean LOS of 9.0 (SD=10.5) days. Discharge to an in-patient rehabilitation unit occurred in 22% of patients after mild TBI and in 61% of patients after moderate/severe TBI. About half of patients age 65-74 years (49%) and age 75-84 years (48%) were admitted to an ICU with a mean of respectively 10 (SD=11) and 8 (SD=10) days and 20% of persons aged ≥85 years were admitted to an ICU with a mean of 6 days (SD=6). Of males, 51% were admitted to an ICU with the LOS of 10 days (SD=11) and of females, 37% with a LOS of 8 days (SD=9). Of patients who survived discharge (n=1056), 30%

of older adults received in-patient rehabilitation care and 12% received out-patient rehabilitation care. Of patients after mild TBI, 22% and of patients after moderate/severe TBI, 61% received in-patient rehabilitation care in the first six months after injury

Outcomes of older patients after TBI

Of 722 patients with mild TBI, 9% died within six months compared to 60% of 320 patients with moderate/severe TBI (T**able 3**). Around 30% of patients with mild and 83% of patients with moderate/severe TBI had a poor functional outcome (GOSE ≤ 4). Of patients with mild or moderate/severe TBI, respectively 41% and 42% had impaired physical HRQoL scores and 22% and 21% had impaired mental HRQoL scores. Elevated symptoms of PTSD, depression and anxiety were present in respectively 5%, 15% and 9% of patients with mild TBI and 6%, 11% and 9% of patients after moderate/severe TBI.

Of patients aged 65-74 years, 75-85, and ≥85 years, respectively 19%, 31% and 37% died within six months post-injury. For all outcomes, the differences in outcome between 65-74 years and ≥85 years were statistically significant, with lower GOSE and HRQoL (SF-12v2 PCS, SF-12v2 MCS, QOLIBRI-OS) scores and higher PCL-5, PHQ-9, and GAD-7 scores for patients aged 85 years and older (Supplementary Figure 1; post-hoc pairwise comparison: **Supplementary Table 2**). The largest difference by age was observed for SF-12v2 PCS with median scores of 46.7 (37.1-52.4) for patients aged 65-74 years, 40.2 (30.6-46.7) for patients aged 75-84 years and 34.7 (24.9-43.6) for patients ≥85 years ($p<0.001$).

Determinants of outcomes of older patients after TBI

For six-month outcomes, missing values varied from 14% for GOSE to 57%-59% for other outcomes (**Supplementary Table 3).** In multi-variable analyses, lower educational level and pre-injury psychiatric conditions were associated with worse functional outcome, HRQoL and psychological problems (**Table 4, univariable: Supplementary Tables 4-6)**. Severe systemic disease was associated with all outcomes except for GAD-7 scores. Higher age was associated with poorer functional outcome (OR (25%:75%) = 0.54, $CI_{95\%}$ [0.44, 0.67] for ordinal GOSE), and SF-12v2 PCS (B (25%:75%) = -3.22, $CI_{95\%}$ [-4.83,-1.62]) but was not significantly associated with other outcomes (Table 4) . Female sex was associated with lower SF-12v2 PCS (B = -2.03, $CI_{95\%}$ [-3.84,-0.01]) and SF-12v2 MCS (B = -2.11, $CI_{95\%}$ [4.05, -0.18]) and higher PHQ-9 (B = 1.12, $CI_{95\%}$ [0.21,2.04]) and GAD-7 (B = 0.99, $CI_{95\%}$ [0.25,1.72]) scores (Table 4). Patients with a higher GCS were more likely to have a higher GOSE (OR (11:15) 2.31, $CI_{95\%}$ [1.95,2.73] for ordinal GOSE; Table 4). There was no significant association between living situation, prior TBI and beta-blocker use with any of the outcomes. The c-statistic of the GOSE ordinal logistic

regression model was 0.79. The R^2 for the linear regression models ranged from 0.08 to 0.19 (**Table 4**).

Discussion

We aimed to describe the health care utilization and six-month functional, physical, and mental health of patients aged 65 years and older after TBI. Approximately a third of the TBI patients, consisting mostly of moderate and severe TBI patients, received in-patient rehabilitation. Furthermore, the majority of patients reported remaining disability after 6 months, especially in the functional and physical domain. However, of patients who survived, a substantial number of older patients recovered fully or partially to pre-injury health. HRQoL and mental health symptoms were comparable between patients with mild or moderate/severe TBI. Age and measures of injury severity were primarily associated with functional outcome and physical HRQoL. Systemic disease, pre-injury psychiatric conditions, and lower educational level were predictors of functional impairment, lower HRQoL and mental health 6 months post-injury.

Notably, nearly half of all patients aged ≥ 65 years were admitted to an ICU. An explanation for this relatively high percentage could be inclusion of the entire spectrum of TBI severities and recruitment from large university hospitals and specialized trauma referral centres in the CENTER-TBI study [25]. The mortality rate in older adults (≥65 years) was more than three times as high compared to the younger TBI population (<65 years), which is supported by other studies which found that TBI-related deaths are more likely in older age groups [11, 40, 41]. The mortality rate was especially high after moderate/severe TBI (60%), which may be explained by complications, chronic disease, restricted surgical treatment, extra-cranial injuries or biological ageing [42].

The rehabilitation needs in the older TBI population are high and there is a high prevalence of unmet rehabilitation needs [43, 44]. Our study showed that just over 60% of the patients after moderate/severe TBI and 22% of patients after mild TBI received inpatient rehabilitation. Previous research reported that older adults received less intensive rehabilitation services than younger patients [21]. However, multiple studies have shown that (aggressive) treatment and rehabilitation benefits older adults, resulting in functional gain and a higher change of being able to return home [45-47]. It is suggested that a presumed poor outcome in older adults leads to reduced management intensity, which subsequently leads to a higher mortality risk [48].

While the mortality and morbidity rates were high, nearly half of older adults with mild TBI still returned to pre-injury functioning and 20% of older adults after moderate/severe TBI did not report severe disability or death. Additionally, health-related quality of life and mental health symptoms were comparable between older patients with mild or moderate/severe TBI.

Impaired mental and disease specific HRQoL were seen in nearly a quarter of older patients, which is comparable to the general TBI population [25]. Impaired physical HRQoL were found in 40% of older TBI patients which is considerably higher than the 29% found in the general TBI population [25]. This could be explained by a higher occurrence of pre-existing comorbidities, a worse pre-injury functional status and physical frailty in older adults. In CENTER-TBI, older adults do not seem to have higher proportions of depression and anxiety than TBI adults in general [49]. This is consistent to previous studies, which found that older adults report less psychological distress than younger adults [14]. However, the proportion of patients with severe depression and anxiety symptoms is higher than in the general population without TBI [50, 51]. These long-term impairments in a considerable proportion of older TBI patients underline the importance of appropriate follow-up and treatment of older patients with disability after TBI.

Research on outcome following TBI in older adults has predominantly focused on subgroups of TBI severity and functional outcome [14]. In CENTER-TBI, we found that age and injury characteristics were associated with lower functional outcome but were not significant predictors of mental HRQoL and psychological symptoms when controlled for other important factors. This indicates that older age alone is not sufficient when we want to predict and understand outcomes in older TBI patients, which is in line with previous research suggesting that measures of pre-injury functioning and frailty are more strongly associated with the outcome than the age [12]. One previous study on prognostic factors of poor recovery after TBI in older adults suggested that recovery may be associated more with psychosocial than with biomedical or injury factors [52]. Additionally, previous studies in the adult mild TBI population and the older adult general injury population, showed that those with pre-injury morbidity recovered more slowly [53, 54], which is consistent with our findings. These results can eventually be used for targeted rehabilitation programs and prognostic models in order to improve patient outcome. Detailed assessment, inclusion of socio-economic characteristics and pre-injury physical and mental health factors would help to identify older adults with a higher risk of poor outcomes after TBI, who should be monitored and provided early interventions.

This study included a large data sample from multiple European countries in which long-term outcome after TBI in older adults were examined. A variety of both health outcomes and predictors were assessed, including medical history and pharmacotherapy. We also recognize several limitations of our study. First, there are several unmeasured factors including pre- and post-injury frailty, pre-injury HRQoL, mental health at the time of injury, social support and type and frequency of interventions which could be of importance for prediction of outcome in the

older population. Moreover, it could explain why the models for mental health domain do not have a high proportion of explained variance.

Second, for several outcome measures at six-months the proportion of missing values was high. Non-responders were older, reported higher pre-injury morbidity, ISS, and GCS and were more likely to be admitted to the ICU. Non-response could therefore be related to the inability to complete the questionnaire due to generally worse pre-injury health, cognitive impairment, or language difficulties. In addition, patients with severe pre-existing neurological disorder were not included.[25] Thus, a subgroup of older patients with profound disabilities was potentially underrepresented, which may be particularly relevant for the moderate/ severe group with a very low response rate. This highlights the importance of adapting the assessments to older patients and patients with disabilities to facilitate their response. Third, this study only included patients with an indication for CT and who presented to university hospitals and specialized trauma centers, which could limit generalizability to older patients with minor TBIs. Finally, the recruitment of patients was not consecutive but influenced by logistic considerations, which might introduced some bias [25].

Conclusions

With an ageing population, the number of older patients who sustain TBI through incidental falls or road traffic incidents will increase, resulting in rising health care utilization and costs, functional impairment, and physical and mental health problems among older adults. There is a need to study TBI in older adults and to develop consensus on management guidelines for this population. This study reported a high mortality rate and a substantial rate of impairments and disabilities following TBI, especially in the functional and physical domain. Nonetheless, a substantial number of older patients recovers to pre-injury health or reports symptoms rates comparable to the general TBI population. The older patients who survive after TBI should receive the treatment and rehabilitation care to help them regain pre-injury health. Moreover, our study found that patient characteristics, including pre-injury systemic disease, pre-injury psychiatric conditions, and lower educational level are important predictors of poorer outcomes. These results underline the importance of a health care assessment in which these predictors are measured. An important overall implication for management of TBI patients in the acute stage is that there should not be pessimism about outcomes in older adults who survive, among which a substantial number fully or partially return to their preinjury functioning.

Ethics approval

The CENTER-TBI study has been conducted in accordance with all relevant laws of the EU if directly applicable or of direct effect, and all relevant laws of the country where the Recruiting sites were located, including, but not limited to, the relevant privacy and data protection laws and regulations (the "Privacy Law"), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ("ICH GCP") and the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects". Ethical approval was obtained for each recruiting site. Informed Consent was obtained for all patients recruited in the Core Dataset of CENTER-TBI and documented in the e-CRF. The list of sites, Ethical Committees, approval numbers and approval dates can be found on the official Center TBI website (www.center-tbi.eu/project/ethical-approval).

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Declaration of interest

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Table 1. Characteristics of the older adult TBI population in the CENTER-TBI study by response status at six months.

Variable	**Total population**	Responders*	Non-responders	Deceased	**Responders vs. Non-responders**	**Responders vs. deceased**
N	N=1254	N=554	N=423	N=277	p-value	p-value
Age, median (IQR)	74 (69-80)	73 (68-78)	75 (69-81)	76 (71-82)	<0.001	<0.001
65-74 years	634 (50.6%)	318 (57.4%)	209 (49.4%)	107 (38.6%)		
75-84 years	479 (38.2%)	193 (34.8%)	158 (37.4%)	128 (46.2%)		
≥85 years	141 (11.2%)	43 (7.8%)	56 (13.2%)	42 (15.2%)		
Sex, male, n (%)	741 (59.1%)	320 (57.8%)	234 (55.3%)	187 (67.5%)	0.445	0.007
Living alone, n (%)	364 (29.0%)	157 (28.3%)	150 (35.5%)	57 (20.6%)	0.016	0.016
Missing, n (%)	4 (0.3%)	1 (0.2%)	2 (0.5%)	1 (0.4%)		
Highest educational level					<0.001	0.006
Primary school	254 (20.3%)	120 (21.7%)	96 (22.7%)	38 (13.7%)		
Secondary school	272 (21.7%)	128 (23.1%)	105 (24.8%)	39 (14.1%)		
Post-high school training	172 (13.7%)	96 (17.3%)	60 (14.2%)	16 (5.8%)		
College/university	173 (13.8%)	118 (21.3%)	41 (9.7%)	14 (5.1%)		
Missing, n (%)	383 (30.5%)	92 (16.6%)	121 (28.6%)	170 (61.4%)		
Pre-injury ASA-PS class, n (%)					0.034	<0.001
Healthy	256 (20.4%)	142 (25.6%)	78 (18.4%)	36 (13.0%)		
Mild systemic disease	659 (52.6%)	287 (51.8%)	234 (55.3%)	138 (49.8%)		
Severe systemic disease/threat to life	300 (23.9%)	118 (21.3%)	101 (23.9%)	81 (29.2%)		
Missing, n (%)	39 (3.1%)	7 (1.3%)	10 (2.4%)	22 (7.9%)		
Pre-injury physical conditions, n (%)					0.245	0.276
None	133 (10.6%)	66 (11.9%)	44 (10.4%)	23 (8.3%)		
1	275 (21.9%)	130 (23.5%)	91 (21.5%)	54 (19.5%)		
2	296 (23.6%)	140 (25.3%)	92 (21.7%)	64 (23.1%)		
3	236 (18.8%)	99 (17.9%)	78 (18.4%)	59 (21.3%)		
4 or more	299 (23.8%)	119 (21.5%)	115 (27.2%)	65 (23.5%)		
Missing, n (%)	15 (1.2%)	0 (0%)	3 (0.7%)	12 (4.3%)		
Pre-injury psychiatric condition, n (%)	164 (13.1%)	60 (10.8%)	63 (14.9%)	41 (14.8%)	0.034	0.034
Missing, n (%)	47 (3.7%)	4 (0.7%)	18 (4.3%)	25 (9.0%)		
Prior TBI, n (%)	107 (8.5%)	50 (9.0%)	40 (9.5%)	17 (6.1%)	0.694	0.444
Missing, n (%)	122 (9.7%)	29 (5.2%)	35 (8.3%)	58 (20.9%)		
Intracranial traumatic abnormality, n (%)	647 (51.6%)	287 (51.8%)	185 (43.7%)	175 (63.2%)	0.110	<0.001
Missing, n (%)	196 (15.6%)	56 (10.1%)	68 (16.1%)	72 (26.0%)		
Anticoagulants and platelets aggregation inhibitor use, n (%)					0.741	<0.001

Anticoagulant	225 (17.9%)	87 (15.7%)	77 (18.2%)	61 (22.0%)		
Platelet aggregation inhibitor	325 (25.9%)	148 (26.7%)	96 (22.7%)	81 (29.2%)		
Both	25 (2.0%)	8 (1.4%)	8 (1.9%)	9 (3.2%)		
No	618 (49.3%)	303 (54.7%)	216 (51.1%)	99 (35.7%)		
Missing, n (%)		8 (1.4%)	26 (6.1%)	27 (9.7%)		
Beta blocker use, n (%)	314 (25.0%)	131 (23.6%)	105 (24.8%)	78 (28.2%)	0.362	<0.001
Missing, n (%)	93 (7.4%)	16 (2.9%)	34 (8.0%)	43 (15.5%)		
Care pathway, n (%)					0.015	<0.001
ER	209 (16.7%)	127 (22.9%)	76 (18.0%)	6 (2.2%)		
Hospital ward	493 (39.3%)	254 (45.8%)	176 (42.3%)	60 (21.7%)		
ICU	552 (44.0%)	173 (31.2%)	168 (39.7%)	211 (76.2%)		
TBI Severity, n (%)					0.005	<0.001
Mild (GCS 13-15)	862 (68.7%)	468 (84.5%)	326 (78.9%)	68 (24.5%)		
Moderate/Severe (GCS 3-12)	355 (28.3%)	77 (13.9%)	87 (21.1%)	191 (69.0%)		
Missing, n (%)	37 (3.0%)	9 (1.6%)	10 (2.4%)	18 (6.5%)		
Injury mechanism					0.080	0.729
Falls	837 (66.7%)	358 (64.6%)	302 (71.4%)	177 (63.9%)		
Road traffic accident	284 (22.6%)	136 (24.5%)	83 (19.6%)	65 (23.5%)		
Other	133 (10.6%)	60 (10.8%)	38 (9.0%)	38 (9.0%)		
ISS, median (IQR)	16 (9-25)	13 (8-21)	13 (8-25)	26 (20-43)	0.079	<0.001

IQR: inter quartile range, ASA-PS class: American Society of Anesthesiologists Physical Status classification, TBI: Traumatic Brain Injury, GCS = Glasgow Coma Scale, ISS= Injury Severity Score, MVA: motor vehicle accident

**patients who completed at least one questionnaire (SF-12v2, QOLIBRI-OS, PCL-5, PHQ-9, GAD-7) at six months post-injury*

[a] *response vs non-response*

[b] *response vs deceased*

Table 2. Hospital admission and in- and out-patient rehabilitation services for older adults in CENTER-TBI study

	Ward		ICU		six-month in-patient rehabilitation[a]	six-month out-patient rehabilitation[a]
	Patients admitted to a ward, N (%)[b]	Mean number of days (SD)*	Patients admitted to an ICU, N (%)[c]	Mean number of days (SD)*	N (%)[d]	N (%)[e]
Total	817 (65.4)	9.6 (15.0)	566 (45.3)	9.0 (10.5)	285 (29.3)	117 (12.2)
Age						
65-74 years	408 (64.7)	9.3 (11.4)	306 (48.5)	10.0 (10.9)	139 (26.4)	73 (14.0)
75-84 years	322 (67.2)	10.4 (19.0)	231 (48.2)	8.2 (10.1)	124 (35.3)	42 (12.1)
≥85 years	87 (62.6)	8.0 (12.0)	29 (20.9)	5.7 (6.1)	22 (23.2)	2 (2.2)
Sex						
Male	490 (66.4)	10.2 (13.9)	375 (50.8)	9.8 (10.9)	165 (29.4)	61 (10.9)
Female	327 (64.0)	8.6 (16.4)	191 (37.4)	7.5 (9.4)	120 (29.3)	56 (14.0)
Injury mechanism						
Fall	547 (65.6)	8.6 (15.1)	319 (38.2)	8.2 (10.0)	174 (26.4)	70 (10.8)
Road traffic incident	199 (70.3)	10.8 (11.7)	171 (60.4)	9.4 (10.5)	84 (38.9)	39 (18.1)
Other	71 (53.8)	13.4 (20.5)	76 (57.6)	11.5 (11.9)	27 (27.6)	8 (8.2)
Pre-injury ASA-PS class, n (%)						
Healthy	182 (71.7)	8.0 (10.6)	114 (44.9)	10.0 (11.8)	51 (23.4)	38 (17.5)
Mild systemic disease	429 (65.1)	9.6 (13.0)	292 (44.3)	8.8 (10.3)	155 (29.8)	57 (11.1)
Severe systemic disease/threat to life	192 (64.6)	10.5 (21.0)	127 (42.8)	8.8 (10.0)	70 (32.3)	22 (10.4)
TBI Severity, n (%)						

Mild (GCS 13-15)	858 (70.2)	8.3 (15.0)	222 (25.9)	7.6 (10.2)	170 (22.0)	86 (11.3)
Moderate/Severe (GCS 3-12)	197 (55.6)	13.4 (14.4)	318 (89.8)	9.9 (10.4)	112 (60.9)	29 (15.8)

**Length of hospital stay for those patients admitted to a ward/ICU*

[a] *Based on patients who survived discharge (n=1056)*

[b] *5 (0.4%) missing values*

[c] *5 (0.4%) missing values*

[d] *84 (8.0%) missing values*

[e] *97 (9.2%) missing values*

Table 3. Distribution of outcome variables for the total population of older adults after TBI and by TBI severity

	Total	TBI severity*		p-value
		Mild	Moderate/ Severe	
Functional outcome at 6 months				
GOSE	**n=1073/1254**	***n=722/862***	***n=320/355***	<0.001
1 (dead)	277 (25.8%)	68 (9.4%)	191 (59.7%)	
3 (vegetative state/lower severe disability)	120 (11.2%)	65 (9.0%)	54 (16.9%)	
4 (upper severe disability)	56 (5.2%)	43 (6.0%)	12 (3.8%)	
5 (lower moderate disability)	47 (4.4%)	37 (5.1%)	10 (2.8%)	
6 (upper moderate disability)	57 (5.3%)	48 (5.6%)	9 (2.8%)	
7 (lower good recovery)	175 (16.3%)	147 (20.4%)	26 (8.1%)	
8 (upper good recovery)	341 (27.2%)	314 (43.5%)	18 (5.6%)	
HRQoL at 6 months				
SF-12v2 PCS	***(n=541/1254)***	***n=461/862***	***n=71/355***	
Impaired SF-12v2 physical score (<40)	218 (40.3%)	187 (40.6%)	30 (42.3%)	0.787
Median (IQR)	43.3 (34.1-50.5)	43.3 (34.6-50.8)	42.3 (31.8-49.8)	0.315
SF-12v2 MCS	***(n=541/1254)***	***n=461/862***	***n=71/355***	
Impaired SF-12v2 mental score (<40)	117 (21.6%)	102 (22.1%)	15 (21.1%)	0.850
Median (IQR)	50.8 (42.1-58.3)	51.2 (42.0-58.3)	49.3 (41.8-58.2)	0.680
QOLIBRI-OS	***(n=544/1254)***	***n=460/862***	***n=75/355***	
Impaired QOLIBRI-OS (<52)	121 (22.2%)	102 (22.2%)	18 (24.0%)	0.725
Median (IQR)	71.0 (54.0-79.0)	71.0 (54.0-82.0)	67 (54.0-79.0)	0.253
Mental health symptoms at 6 months				
PTSD, PCL-5	***(n=515/1254)***	***n=439/862***	***n=68/355***	
PTSD, PCL-5 ≥33	24 (4.7%)	20 (4.6%)	4 (5.9%)	0.632
Median (IQR)	5.0 (1.0-12.0)	5.0 (2.0-12.0)	6.0 (1.0-13.8)	0.406
Depression, PHQ-9	***(n=519/1254)***	***n=439/862***	***n=71/355***	0.077
None	331 (63.8%)	283 (64.5%)	40 (56.3%)	
Mild	114 (22.0%)	90 (20.5%)	23 (32.4%)	
Moderate/Severe	74 (14.3%)	66 (15.0%)	8 (11.3%)	
Median (IQR)	3.0 (1.0-7.0)	3.0 (1.0-6.0)	3.0 (1.0-7.0)	0.650
Anxiety, GAD-7	***(n=515/1254)***	***n=436/862***	***n=70/355***	0.944
None	392 (76.1%)	329 (75.5%)	54 (77.1%)	
Mild	79 (15.3%)	69 (15.8%)	10 (14.3%)	
Moderate/Severe	44 (8.5%)	38 (8.7%)	6 (8.6%)	
Median (IQR)	1.0 (0.0-4.0)	1.0 (0.0-4.0)	1.0 (0.0-4.0)	0.897

Cut-off values: SF-12v2 PCS and SF-12v2 MCS < 40, QOLIBRI < 52, PCL-5 ≥ 33, PHQ-9 ≥ 10, GAD-7 ≥ 10; SF-12 PCS = Short Form (12) Health Survey (physical component score); SF-MCS = Short Form (12) Health Survey (mental component score); QOLIBRI = Quality of Life after Brain Injury

**Glasgow Coma Score (GCS) is missing for 37 (3.0%) patients*

Table 4. Multivariable regression analyses: Odds ratios (OR) for global functional outcome (GOSE), and regression coefficients (B) for generic HRQoL (SF-12v2), disease-specific HRQoL (QOLIBRI-OS), and post-traumatic stress (PCL-5), depression (PHQ-9) and anxiety (GAD-7) symptoms.

	Global functional outcome *	Health-related quality of life *			Psychological symptoms**		
Predictor	**GOSE (1-8) (OR, CI 95%)**	**SF-12 PCS (B, CI 95%)**	**SF-12 MCS (B, CI 95%)**	**QOLIBRI-OS (B, CI 95%)**	**PCL-5 (B, CI 95%)**	**PHQ-9 (B, CI 95%)**	**GAD-7 (B, CI 95%)**
Age [1]	**0.54 [0.44;0.67]**	**-3.22 [-4.83;-1.62]**	-0.44 [-2.17;1.29]	-2.34 [-5.71;1.03]	-0.04 [-1.86;1.77]	0.42 [-0.39;1.23]	0.01 [-0.66;0.68]
Female sex	1.08 [0.84;1.39]	-2.03 [-3.84;-0.01]	-2.11 [-4.05;-0.18]	-3.15 [-6.88;0.59]	1.75 [-0.27;3.78]	1.12 [0.21;2.04]	**0.99 [0.25;1.72]**
High school vs. Primary school	1.18 [0.82;1.71]	2.50 [-0.01;5.01]	**3.69 [1.02;6.37]**	**7.74 [2.59;12.89]**	-3.41 [-6.19;-0.63]	**-1.86 [-3.17;-0.55]**	**-2.12 [-3.20;-1.04]**
Post-high school vs. Primary s.	1.18 [0.81;1.73]	0.96 [-1.65;3.56]	1.02 [-2.12;4.16]	2.49 [-3.66;8.64]	0.05 [-3.13;3.23]	-0.21 [-1.56;1.14]	-1.25 [-2.50;0.01]
College/University vs. Primary s.	1.49 [1.00;2.21]	**4.90 [2.32;7.47]**	3.33 [0.53;6.12]	**6.87 [1.03;12.71]**	-3.15 [-6.20;-0.11]	**-1.81 [-3.14;-0.47]**	**-1.84 [-3.09;-0.59]**
Living alone	1.15 [0.88;1.52]	-0.17 [-2.16;1.81]	-0.73 [-2.83;1.37]	-1.74 [-5.75;2.28]	-1.24 [-3.41;0.94]	0.33 [-0.65;1.31]	-0.65 [-1.44;0.14]
Mild disease vs. Healthy	0.75 [0.55;1.04]	-2.52 [-4.70;-0.35]	-2.51 [-4.82;-0.21]	-5.59 [-10.03;-1.14]	2.14 [-0.24;4.52]	0.77 [-0.30;1.84]	-0.22 [-1.08;0.64]
Severe disease vs. Healthy	**0.53 [0.36;0.79]**	**-5.30 [-8.16;-2.44]**	**-6.13 [-9.15;-3.10]**	**-15.9 [-21.66;-10.14]**	**4.14 [0.95;7.32]**	**2.06 [0.63;3.49]**	0.50 [-0.64;1.64]
Pre-injury psychiatric conditions	**0.54 [0.38;0.76]**	-3.19 [-5.98;-0.40]	**-7.73 [-10.70;-4.75]**	**-11.93 [-17.62;-6.25]**	**5.38 [2.25;8.52]**	**3.80 [2.37;5.23]**	**2.44 [1.29;3.58]**
Prior TBI	1.27 [0.82;1.98]	1.30 [-1.83;4.44]	2.93 [-0.37;6.23]	0.54 [-5.91;6.98]	-2.82 [-6.18;0.54]	-0.45 [-1.98;1.08]	-0.99 [-2.17;0.19]
Anticoagulants/PAI use	0.76 [0.57;1.00]	-2.26 [-4.25;-0.26]	1.48 [-0.64;3.60]	-0.65 [-4.68;3.38]	-0.18 [-2.39;2.03]	-0.02 [-1.02;0.97]	0.43 [-0.36;1.23]
Beta blocker use	0.80 [0.60;1.07]	-1.68 [-3.90;0.54]	0.73 [-1.57;3.04]	-0.39 [-4.85;4.07]	-0.95 [-3.34;1.44]	-0.49 [-1.59;0.60]	-0.31 [-1.18;0.55]
Intracranial abnormalities	**0.55 (0.42;0.72)**	-0.80 [-2.68;1.08]	0.33 [-1.67;2.33]	-3.99 [-7.81;-0.18]	-0.25 [-2.36;1.86]	0.37 [-0.59;1.33]	0.17 [-0.63;0.97]
Road traffic incident vs. Falls	0.97 [0.72;1.30]	-0.49 [-2.57;1.60]	-1.22 [-3.44;0.99]	-1.61 [-5.86;2.64]	2.20 [-0.11;4.51]	0.28 [-0.76;1.31]	0.32 [-0.52;1.15]
Other vs. Falls	0.81 [0.54;1.23]	-0.47 [-3.29;2.36]	-1.84 [-4.87;1.18]	-2.73 [-8.52;3.05]	3.22 [0.01;6.42]	0.43 [-1.01;1.88]	0.61 [-0.54;1.76]
Glasgow Coma Score (GCS) [1]	**2.31 [1.95;2.73]**	0.55 [-0.83;1.92]	-0.39 [-1.86;1.08]	2.45 [-0.31;5.20]	0.48 [-1.11;2.06]	-0.03 [-0.72;0.67]	0.15 [-0.43;0.73]
Injury severity score (ISS) [1]	**0.50 [0.41;0.60]**	-1.43 [-2.84;-0.01]	**-2.49 [-4.00;-0.99]**	-1.32 [-4.17;1.53]	**2.43 [0.85;4.01]**	0.71 [0.00;1.42]	0.52 [-0.04;1.08]
Measure of performance	C-statistic 0.79	Adjusted R^2 0.19	Adjusted R^2 0.12	Adjusted R^2 0.15	Adjusted R^2 0.08	Adjusted R^2 0.12	Adjusted R2 0.10

*[1]Continuous predictors scaled by interquartile range that compares the 1st quartile and the 3rd quartile. * Higher score=better outcome. ** Higher score= worse outcome.*

A p-value <0.05 and a p-value <0.01.

GAD-7 = Generalized Anxiety Disorder questionnaire; GOSE = Glasgow Outcome Scale—Extended; PAI=platelets aggregation inhibitor PCL-5 = Posttraumatic Stress Disorder Checklist; PHQ-9 = Patient Health Questionnaire; SF-12 PCS = Short Form (12) Health Survey (physical component score); SF-MCS = Short Form (12) Health Survey (mental component score); QOLIBRI = Quality of Life after Brain Injury