Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI

Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study

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Summary

Background The burden of traumatic brain injury (TBI) poses a large public health and societal problem, but the characteristics of patients and their care pathways in Europe are poorly understood. We aimed to characterise patient case-mix, care pathways, and outcomes of TBI.

Methods CENTER-TBI is a Europe-based, observational cohort study, consisting of a core study and a registry. Inclusion criteria for the core study were a clinical diagnosis of TBI, presentation fewer than 24 h after injury, and an indication for CT. Patients were differentiated by care pathway and assigned to the emergency room (ER) stratum (patients who were discharged from an emergency room), admission stratum (patients who were admitted to a hospital ward), or intensive care unit (ICU) stratum (patients who were admitted to the ICU). Neuroimages and biospecimens were stored in repositories and outcome was assessed at 6 months after injury. We used the IMPACT core model for estimating the expected mortality and proportion with unfavourable Glasgow Outcome Scale Extended (GOSE) outcomes in patients with moderate or severe TBI (Glasgow Coma Scale [GCS] score ≤12). The core study was registered with ClinicalTrials.gov, number NCT02210221, and with Resource Identification Portal (RRID: SCR_015582).

Findings Data from 4509 patients from 18 countries, collected between Dec 9, 2014, and Dec 17, 2017, were analysed in the core study and from 22 782 patients in the registry. In the core study, 848 (19%) patients were in the ER stratum, 1523 (34%) in the admission stratum, and 2138 (47%) in the ICU stratum. In the ICU stratum, 720 (36%) patients had mild TBI (GCS score 13–15). Compared with the core cohort, the registry had a higher proportion of patients in the ER (9839 [43%]) and admission (8571 [38%]) strata, with more than 95% of patients classified as having mild TBI. Patients in the core study were older than those in previous studies (median age 50 years [IQR 30–66], 1254 [28%] aged >65 years), 462 (11%) had serious comorbidities, 772 (18%) were taking anticoagulant or antiplatelet medication, and alcohol was contributory in 1054 (25%) TBIs. MRI and blood biomarker measurement enhanced characterisation of injury severity and type. Substantial inter-country differences existed in care pathways and practice. Incomplete recovery at 6 months (GOSE <8) was found in 207 (30%) patients in the ER stratum, 665 (53%) in the admission stratum, and 1547 (84%) in the ICU stratum. Among patients with moderate-to-severe TBI in the ICU stratum, 623 (55%) patients had unfavourable outcome at 6 months (GOSE <5), similar to the proportion predicted by the IMPACT prognostic model (observed to expected ratio 1·06 [95% CI 0·97–1·14]), but mortality was lower than expected (0·70 [0·62–0·76]).

Interpretation Patients with TBI who presented to European centres in the core study were older than were those in previous observational studies and often had comorbidities. Overall, most patients presented with mild TBI. The incomplete recovery of many patients should motivate precision medicine research and the identification of best practices to improve these outcomes.

Funding European Union 7th Framework Programme, the Hannelore Kohl Stiftung, OneMind, and Integra LifeSciences Corporation.

Lancet Neurol 2019; 18: 923–34

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Introduction

The burden of traumatic brain injury (TBI) is widely recognised as a large public health and societal problem. TBI results in 1·5 million hospital admissions and 57 000 deaths in the EU each year,[1] but the landscape of TBI in European hospitals is poorly characterised. In November, 2017, a Commission in *The Lancet Neurology*[2] on TBI highlighted the burden posed by TBI to patients, relatives, and society, and provided recommendations to improve patient outcomes through improved prevention, clinical care, and research. One recommendation was for large collaborative observational studies to collect

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See Online for appendix

For more on **CENTER-TBI** see www.center-tbi.eu

For more on **InTBIR** see https://intbir.nih.gov/

Research in context

Evidence before this study

In November, 2017, the Commission on *Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research* in *The Lancet Neurology* highlighted existing deficiencies in epidemiology and patient characterisation. An extensive literature search was undertaken as a basis for writing the Commission, which went beyond the academic literature and included national and international policy documents and statistical resources. These data were updated through more focused literature reviews for this manuscript. The Commission concluded that concerted efforts are urgently needed to address deficiencies in prevention, care, and research, and recommended that large collaborative studies be done, which could provide the framework for precision medicine and comparative effectiveness research.

Added value of this study

The CENTER-TBI registry and core study provide detailed insights into the contemporary landscape of traumatic brain injury (TBI) in Europe and constitute a unique resource for improving the characterisation of TBI, developing precision medicine approaches, and identification of best practices. The epidemiology of TBI as observed in the CENTER-TBI core study and registry differs from previous observational studies: patients were older, were most commonly injured by a fall, and many had comorbidities. Advanced neuroimaging and blood biomarkers can improve characterisation of injury type and severity. Differentiation of patients by care pathways provided novel insights. Around 95% of patients discharged from the emergency room or admitted to the ward, and a third of those primarily admitted to the ICU, had a so-called mild TBI. However, nearly a third of patients discharged from the emergency room and over half of those admitted to the hospital ward did not attain full recovery. There are substantial national and regional variations in care pathways and clinical management in Europe.

Implications of all the available evidence

The results from CENTER-TBI suggest that TBI should no longer be considered predominantly a disease of otherwise healthy young men. Falls were the most common cause of TBI and should motivate an increased focus for prevention. Mild TBI not only poses the greatest societal burden to health care, but also affects functional recovery and quality of life more than was commonly thought. Improved disease characterisation can contribute to precision medicine approaches through the development of multidimensional classifications of initial injury severity and outcome. Variations in care offer an opportunity for comparative effectiveness research to identify best practice.

longitudinal data, which could improve patient characterisation to allow better targeting of therapies and identify best practices through comparative effectiveness research.

The Collaborative European NeuroTrauma Effectiveness Research (CENTER-TBI) project is a European study, done within the InTBIR initiative,[3] that was designed to address these needs.[4] The project includes a multicentre, longitudinal, observational cohort study (core study) with highly granular data collection, which included detailed longitudinal clinical and outcome data, neuroimaging repositories, a DNA repository, and a blood and serum biobank; and a registry, which collected basic administrative data.

The main aims are to: (1) better characterise TBI as a disease and describe it in the European context, and (2) identify the most effective clinical interventions for managing TBI. Provider profiles of participating centres were established to characterise structures and processes of care in preparation for comparative effectiveness research.[5–10] We aim to describe the contemporary landscape of TBI in Europe, with a focus on the patient case-mix, care pathways, and outcomes in the core study, and to explore generalisability by comparison with data from the registry.

Methods

Study design and participants

CENTER-TBI includes a core study and a registry.[4] 65 centres initiated patient enrolment (figure 1). The core study was an observational, longitudinal, cohort study of patients with all severities of TBI, presenting between Dec 19, 2014, and Dec 17, 2017, to centres across Europe and Israel. Inclusion criteria were a clinical diagnosis of TBI, indication for CT scanning, presentation to study centre within 24 h of injury, and informed consent obtained according to local and national requirements.[4] Participants were excluded if they had any severe pre-existing neurological disorder that could confound outcome assessments.

Patients were differentiated by care pathway into three strata: (1) emergency room (ER) stratum (patients assessed in the ER and discharged), (2) admission stratum (admitted to hospital ward), and (3) intensive care unit (ICU) stratum (primary admission to the intensive care unit). The assignment to a stratum was done prospectively in the core study, and retrospectively in the registry. Generalisability of the core study was assessed through comparison with the registry, which collected administrative data not requiring consent and covered a site-specific, convenience-based period during the recruitment period of the core study.

The CENTER-TBI study was done in accordance with all relevant laws of the European Union, if directly applicable or of direct effect, and all laws of the country where the recruiting sites were located, including, but not limited to, the privacy and data protection laws and regulations, the 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

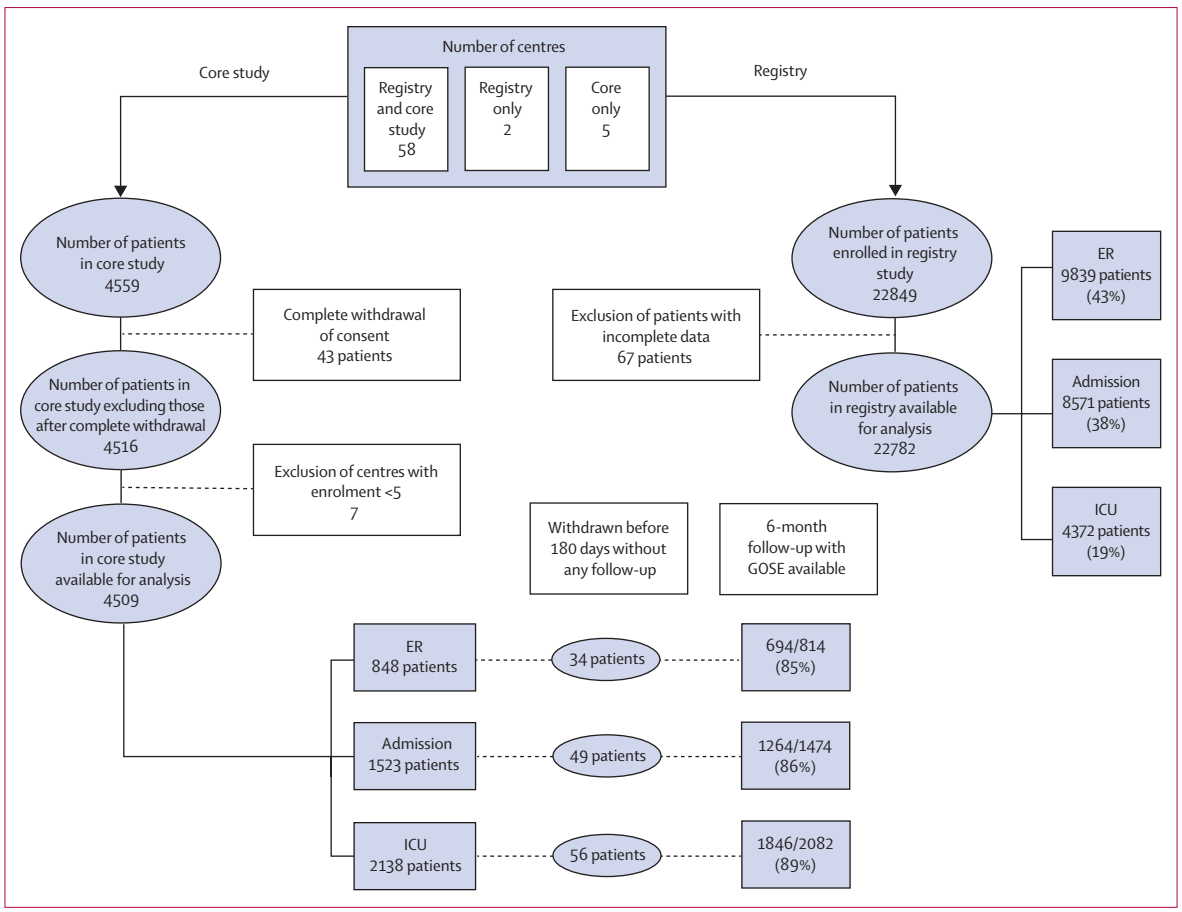

Figure 1: **Trial profile**
The accrual to the emergency room, admission, and intensive care unit strata was defined prospectively in the core study, and retrospectively in the registry. GOSE=Glasgow Outcome Scale Extended.

International Council on Harmonisation guideline on Good Clinical Practice (CPMP/ICH/135/95) and the World Medical Association Declaration of Helsinki. Informed consent by the patients or the legal representative or next of kin was obtained according to the local legislations for all patients recruited in the core dataset of CENTER-TBI and documented in the electronic case report form.

Ethics approval was obtained for each recruiting site. The list of sites, ethics committees, approval numbers, and approval dates is available online.[11]

Outcomes

Outcome assessments were done at 6 months after injury. The primary outcome measures were global function and health-related quality of life using the eight-point Glasgow Outcome Scale (GOSE; overall effect of injury, including extracranial injuries)[12], the quality of life after brain injury overall scale (Qolibri-OS),[13] and the 12-item short form health survey (SF-12v2).[14] Details of data, imaging, biosamples collection and banking, data handling, and analysis are provided in the appendix.

Data collection, handling, and storage

Clinical data were collected using a web-based electronic case report form, with stratum-specific workflows (QuesGen Systems Incorporated, Burlingame, CA, USA). Variables were coded in accordance with the Common Data Elements scheme established by the US National Institutes of Health's National Institute of Neurological Disorders. Blood was banked for DNA extraction and assayed for protein biomarkers (neuron specific enolase [NSE], S100B, neurofilament light, total tau, glial fibrillary acidic protein [GFAP], and ubiquitin carboxyl-terminal hydrolase L1 [UCHL1]). Patients underwent X-ray CT at admission (repeated if clinically indicated), and MRI was obtained in a subset of patients. We provide data on all admission CT examinations, biomarker data on the first 961 patients, and MRI data on the 504 patients who underwent an initial MRI within 3 weeks of injury.

For more on the **Common Data Elements scheme** see https://commondataelements.ninds.nih.gov/

Data handling and storage

Data were de-identified and stored on a secure database, hosted by the International Neuroinformatics Coordinating

For more on the **International Neuroinformatics Coordinating Facility** see https://www.incf.org/

Facility in Stockholm, Sweden. Source data verification of major characteristics was undertaken on a quasi-random sample of 1298 (28%) patients by a designated contract research organisation (ICON, Paris, France). Detailed curation was done by a multidisciplinary data curation task force.

	Overall	ER stratum	Admission stratum	ICU stratum	p value*
Demographic characteristics					
Age (years)	50 (30–66)	48 (29–64)	53 (32–69)	49 (29–65)	0·001
>65 years	1254/4509 (27·8%)	209/848 (24·6%)	493/1523 (32·4%)	552/2138 (25·8%)	
Sex	..	..	..	..	<0·0001
Male	3023/4509 (67·0%)	473/848 (55·8%)	988/1523 (64·9%)	1562/2138 (73·1%)	..
Female	..	..	..	..	..
White	4158/4300 (96·7%)	810/831 (97·5%)	1452/1508 (96·3%)	1896/1961 (96·7%)	0·33
Socioeconomic characteristics					
Years of education (n=3212)	13 (10–16)	13 (11–16)	13 (11–16)	12 (10–15)	<0·0010
Highest level of education	..	..	..	..	<0·0001
College or university	850/3566 (23·8%)	236/787 (30·0%)	334/1304 (25·6%)	280/1475 (19·0%)	..
Married or living with partner	2070/4075 (50·8%)	385/797 (48·3%)	717/1426 (50·3%)	968/1852 (52·3%)	0·15
Employment status before injury	..	..	..	..	0·05
Working	1946/3980 (48·9%)	427/816 (52·3%)	638/1414 (45·1%)	881/1750 (50·3%)	..
Pre-injury health status and medical history					
Pre-injury ASA-PS classification	..	..	..	..	0·56
Patient with mild systemic disease	1410/4373 (32·2%)	268/843 (31·8%)	507/1502 (33·8%)	635/2028 (31·3%)	..
Patient with severe systemic disease	462/4373 (10·6%)	93/843 (11·0%)	159/1502 (10·6%)	210/2028 (10·4%)	..
Previous TBI	402/4158 (9·7%)	120/812 (14·8%)	149/1459 (10·2%)	133/1887 (7·0%)	<0·0001
Anticoagulants	298/4345 (6·9%)	46/837 (5·5%)	133/1510 (8·8%)	119/1998 (6·0%)	<0·0009
Platelet aggregation inhibitors	474/4345 (10·9%)	85/837 (10·2%)	178/1510 (11·8%)	211/1998 (10·6%)	0·38
Cause of injury and influence of alcohol					
Cause of injury	..	..	..	..	<0·0001
Road traffic incident	1682/4388 (38·3%)	266/836 (31·8%)	490/1499 (32·7%)	926/2053 (45·1%)	..
Incidental fall	2024/4388 (46·1%)	424/836 (50·7%)	761/1499 (50·8%)	839/2053 (40·9%)	..
Alcohol involved in the injury (yes or suspected)	..	..	..	..	..
All causes	1054/4163 (25·3%)	137/828 (16·5%)	384/1452 (26·4%)	533/1883 (28·3%)	<0·0001
Road traffic incident	262/1528 (17·1%)	25/260 (9·6%)	76/471 (16·1%)	161/797 (20·2%)	<0·0001
Incidental Fall	533/1918 (27·8%)	72/414 (17·4%)	209/730 (28·6%)	252/774 (32·6%)	<0·0001
Clinical presentation					
GCS	15 (10–15)	15 (15–15)	15 (14–15)	9 (4–14)	<0·0001
Mild (13–15)	2955/4330 (68·2%)	826/832 (99·3%)	1409/1489 (94·6%)	720/2009 (35·8%)	..
Moderate (9–12)	389/4330 (9·0%)	2/832 (0·2%)	59/1489 (4·0%)	328/2009 (16·3%)	..
Severe (3–8)	986/4330 (22·8%)	4/832 (0·5%)	21/1489 (1·4%)	961/2009 (47·8%)	..
Pupillary reactivity	..	..	..	..	<0·0001
One pupil unreactive	164/4247 (3·9%)	3/795 (0·4%)	27/1436 (1·9%)	134/2016 (6·6%)	..
Two pupils unreactive	281/4247 (6·6%)	16/795 (2·0%)	19/1436 (1·3%)	246/2016 (12·2%)	..
Hypoxia (prehospital or ER phase)	299/4256 (7·0%)	3/818 (0·4%)	30/1457 (2·1%)	266/1981 (13·4%)	<0·0001
Hypotension (prehospital or ER phase)	297/4296 (6·9%)	4/820 (0·5%)	26/1484 (1·8%)	267/1992 (13·4%)	<0·0001
Any major extracranial injury (AIS ≥3)	1642/4509 (36·4%)	46/848 (5·4%)	422/1523 (27·7%)	1174/2138 (54·9%)	<0·0001
CT characteristics					
Any intracranial abnormality at local reading	2268/3924 (57·8%)	53/768 (6·9%)	632/1317 (48·0%)	1583/1820 (87·0%)	<0·0001
Any intracranial abnormality at central reading	2434/4037 (60·3%)	103/804 (12·8%)	681/1379 (49·4%)	1650/1854 (89·0%)	<0·0001
MRI characteristics					
Any intracranial abnormality at central reading	312/504 (61·9%)	32/123 (26·0%)	101/180 (56·1%)	179/197 (90·9%)	<0·0001

(Table 1 continues on next page)

	Overall	ER stratum	Admission stratum	ICU stratum	p value*
(Continued from previous page)					
Biomarkers†					
NSE (ng/mlL; n=961)	18 (13–27)	13 (11–16·8)	14 (11–18)	23 (15–34)	<0·0001
S100B (µg/L; n=960)	0·18 (0·09–0·42)	0·07 (0·05–0·12)	0·11 (0·06–0·19)	0·30 (0·15–0·59)	<0·0001
GFAP (ng/mL; n=1010)	4·4 (0·8–17)	0·3 (0·1–1·0)	1·7 (0·6–5·1)	11 (3·4–31)	<0·0001
NFL (pg/mL; n=1010)	23 (10–60)	8·3 (5·1–15)	16 (8–30)	40 (18–95)	<0·0001
Total Tau (pg/mL; n=1010)	4 (1·7–11)	1·2 (0·8–2·0)	2·3 (1·3–4·5)	7·9 (3·3–17)	<0·0001
UCHL1 (pg/mL; n=1009)	127 (48–381)	35 (20–64)	68 (34–122)	275 (109–597)	<0·0001
Laboratory measurements					
Haemoglobin (g/dL; n=3846)	14 (12–15)	14 (13–15)	14 (13–15)	13 (12–14)	<0·0001
Glucose (mmol/L; n=3492)	6·9 (5·9–8·3)	6 (5·3–7·1)	6·5 (5·7–7·8)	7·3 (6·3–8·9)	<0·0001

Data are median (IQR) or n (%), unless otherwise indicated. ER=emergency room. ICU=intensive care unit. TBI=traumatic brain injury. AIS=abbreviated injury score. ASA-PS=American Society of Anesthesiologists physical status classification system. GCS=Glasgow Coma Scale. S100B=S100 calcium-binding protein B. NSE=Neuron-specific enolase. NFL=neurofilament light. GFAP=glial fibrillary acidic protein. UCHL1=ubiquitin carboxy-terminal hydrolase L1. *p values were derived from ANOVA for continuous characteristics and χ^2 statistics for categorical characteristics, comparing strata. The p value assessed compatibility with the null hypothesis of no differences between strata. †NSE and S-100B were measured using the e602 module of a Cobas 8000 analyser (Roche Diagnostics International, Rotkreuz, Switzerland) in Pécs, Hungary; and NFL, total tau, GFAP, and UCHL1 using the Quanterix SIMOA Neurology 4-plex kit (Quanterix, Lexington, MA, USA), at the University of Florida, FL, USA.

Table 1: **Baseline characteristics of patients enrolled in the CENTER-TBI core study**

Statistical analysis

Data (version 2.0) were accessed using a bespoke data management tool, Neurobot (details available on the SciCrunch Resource Identification Portal, using the Research Resource Identifier RRID/SCR_017004). We report completeness of data, medians, and IQRs for continuous or ordinal variables, and numbers and percentages for categorical variables. All analyses were differentiated by stratum and done in R (version 3.5.1) and RStudio (version 1.0.136). ANOVA was used for comparison of continuous variables across strata. The χ^2 test was used for comparison of categorical variables. No corrections for multiple comparisons were done. For comparisons of characteristics between strata, we assessed compatibility with the null hypothesis of no differences between strata. κ statistics were used to express the agreement between central and local radiological assessment of admission CT scans and for CT versus MR scans. We analysed complete outcome data for the primary outcome measures. Analysis of secondary outcome measures (appendix p 4) is ongoing and will be presented elsewhere. For patients with GOSE scores outside the prespecified 5–8-month window (n=988 [22%]), we used a multistate model to impute the 180-day GOSE (msm package[15]). We classified Qolibri-OS scores less than 52 and SF-12v2 summary scores less than 40 as impaired.[16] When there was no SF-12v2 summary score we derived scores using SF-36v2 items when available.

We used the IMPACT core model for the expected mortality and proportion with unfavourable GOSE outcomes among patients with moderate or severe TBI (Glasgow Coma Scale [GCS] score ≤12).[17] Observed mortality and unfavourable GOSE outcomes were compared with expected outcomes and expressed as a ratio with 95% CIs estimated according to a Poisson distribution. The core study is registered with ClinicalTrials.gov, number NCT02210221, and the Resource Identification Portal (RRID: SCR_015582).

For more on **Neurobot** see http://neurobot.incf.org

Role of the funding source

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

Results

We enrolled 4559 patients in the core study and 22 849 patients in the registry from 65 sites in 19 countries. We analysed data from 4509 (98·9%) patients in the core study and 22 782 (99·7%) in the registry obtained from 18 countries (figure 1). The median number of enrolled patients by centre in the core study was 50 (IQR 21–107), with widely different distributions across strata (appendix pp 17, 18). In the core study, 848 (19%) patients in the ER stratum, 1523 (34%) in the admission stratum, and 2138 (47%) were in the ICU stratum. The registry enrolled more patients in the ER and admission strata than did the core study (figure 1).

Overall, the median age was 50 years (IQR 30–66), with 1254 (28%) patients older than 65 years (table 1). Patients in the admission stratum were older (53 years [32–69], 493 [32%] aged >65 years), than were those in the ER and ICU strata. Male patients were overrepresented in every stratum, most notably in the ICU stratum (table 1). At older age, however, the proportion of female patients was higher in the ER and admission strata (appendix p 19). Severe systemic disease was reported in 462 (11%) patients (table 1).

Patients differed between the three strata with respect to socioeconomic characteristics (education, marital, and

	Overall	ER stratum	Admission stratum	ICU stratum	p value*
Referral					
Primary referral	3761/4492 (83·7%)	818/847 (96·6%)	1323/1522 (86·9%)	1620/2123 (76·3%)	<0·0001
Time to study center (min; n=4491)	65 (45–100)	62 (42–105)	60 (41–96)	72 (50–101)	..
Secondary referral	731/4492 (16·3%)	29/847 (3·4%)	199/1522 (13·1%)	503/2123 (23·7%)	<0·0001
Time to study center (min; n=4491)	297 (211–440)	257 (151–316)	295 (205–428)	301 (218–445)	..
Diagnostic and surgical interventions					
Time from injury to first CT (min; n=3924)	118 (81–199)	153 (103–273)	112 (75–190)	110 (80–165)	<0·0001
ICP monitor placed	924/2159 (42·8%)	NA	3	921/2113 (43·6%)	<0·0001
GCS ≤8	591/958 (61·7%)	NA	NA	591/958 (61·7%)	<0·0001
Intracranial surgery	885/3686 (24·0%)	1	64/1521 (4·2%)	820/2124 (38·6%)	<0·0001
Extracranial surgery	735/3685 (19·9%)	1	128/1520 (8·4%)	606/2124 (28·5%)	<0·0001
Length of hospital stay					
Length of stay (days; n=4392)	2·8 (1·0–12)	0·22 (0·14–0·60)	2·0 (0·77–5·0)	11 (3·4–26)	<0·0001
Length of stay for all patients who survived to hospital discharge (days; n=4018)	2·8 (1·0–12)	0·22 (0·14–0·60)	2·0 (1·0–5·0)	13 (5·0–29)	<0·0001
Hospital discharge destination					
Home	2646/4191 (63·1%)	803/807 (99·5%)	1246/1466 (85·0%)	597/1918 (31·1%)	..
Rehabilitation Unit	480/4191 (11·5%)	0/807 (0%)	58/1466 (4·0%)	422/1918 (22·0%)	..
Other Hospital	636/4191 (15·2%)	0/807 (0%)	118/1466 (8·0%)	518/1918 (27·0%)	..
Nursing Home	49/4191 (1·2%)	1/807 (0·1%)	2/1466 (0·1%)	46/1918 (2·4%)	..
Other	17/4191 (0·4%)	0/807 (0%)	0/1466 (0%)	17/1918 (0·9%)	..
In-hospital mortality	363/4191 (8·7%)	3/807 (0·4%)	42/1466 (2·9%)	318/1918 (16·6%)	..

Data are n/N (%) or median (IQR), unless otherwise indicated. ER=emergency room. ICU=intensive care unit. ICP=intracranial pressure. GCS=Glasgow Coma Scale. *p values were derived from ANOVA for continuous characteristics and χ^2 statistics for categorical characteristics, comparing strata. The p value assessed compatibility with the null hypothesis of no differences between strata.

Table 2: **Care pathways in the CENTER-TBI core study**

employment status), medical history (especially frequency of having had a previous TBI), cause of injury, and clinical severity (table 1, appendix pp 6–9). An incidental fall was the most common cause of injury in the ER and admission strata (table 1). We found a clear association with age, with high rates of falls in patients younger than 10 years and in patients older than 65 years (appendix p 20). Road-traffic incidents were most common in the ICU stratum (appendix p 8). Alcohol use was reported in 144 (64%) violence-related TBIs, in 533 (28%) incidental falls, and in 262 (17%) road-traffic incidents (appendix p 21). Recreational and prescription drug use were reported in 203 (6%) patients.

Clinical severity varied by stratum. In the ER and admission strata, the median baseline GCS was 15, and 826 (99%) patients in the ER stratum and 1409 (95%) in the admission stratum were classified as having mild TBI (GCS 13–15; table 1, appendix p 22). In the ICU stratum, the median GCS was 9 (4–14) and 720 (36%) patients had a GCS greater than 12. Major extracranial injuries (abbreviated injury score ≥3) were reported in 422 (28%) patients in the admission stratum and in 1174 (55%) in the ICU stratum. The body region most commonly injured was thorax and chest (n=742 [35%]), and concomitant serious spinal injuries occurred in 374 (18%) patients (appendix p 9).

The differential recruitment to individual strata in the core study and the registry (figure 1), and the exclusion of patients with pre-existing neurological disease from the core cohort, precluded direct overall comparisons between the two cohorts. When differentiated by stratum, patients in the core study broadly resembled those in the registry (appendix p 10). The proportion of patients who had serious extracranial injuries was similar in the core study and the registry in the admission and ICU cohorts (appendix p 10), and a similar proportion of patients in the ICU stratum in both study parts arrived intubated at the ER (appendix p 10). In the ICU stratum, the frequency of emergency surgical procedures was similar (eg, 297 [14%] patients had received craniotomy for haematoma or contusion in the core study *vs* 700 [16%] in the registry; appendix p 10). In-hospital mortality was similar across strata (eg, 318 [15%] patients in the core ICU stratum and 773 [19%] in the registry ICU stratum; appendix p 10). Some differences existed in other baseline and injury characteristics (appendix p 10). Patients in the core ER stratum were more frequently injured in road-traffic incidents and had more intracranial abnormalities on CT scanning than did their registry counterparts (appendix p 10). Patients in the core admission stratum were younger, more often male, more frequently injured in road traffic incidents, and had more intracranial abnormalities on

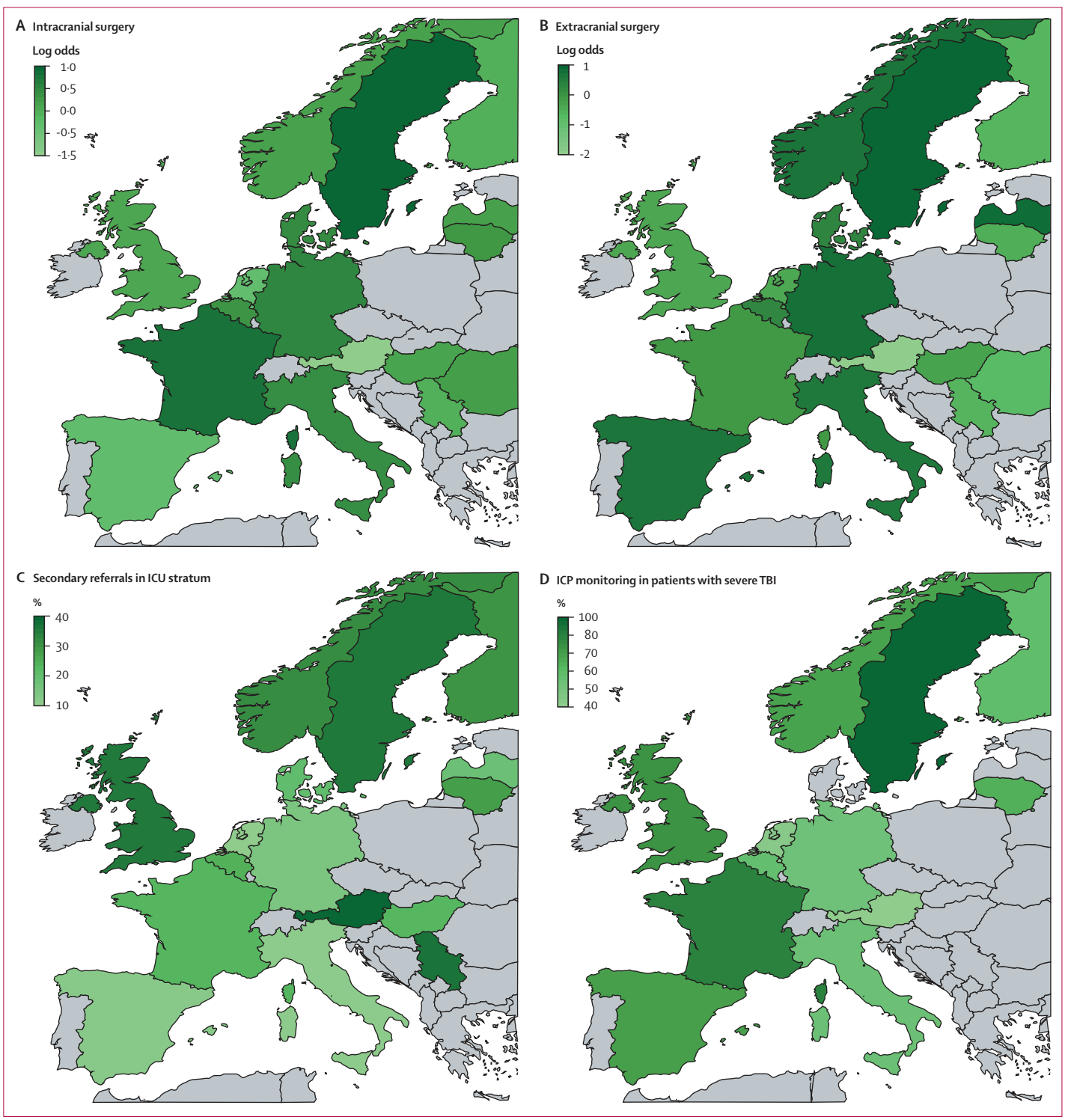

Figure 2: **Between-country differences in processes of care for TBI in Europe**
(A) The log odds ratio of intracranial surgery, representing the log odds of intracranial surgery per contry compared with the overall average, adjusted for IMPACT CT model and stratum. (B) The log odds ratio of extracrianal surgery, representing the log odds of extracranial surgery per country compared with the overall average, adjusted for any major extracranial injury and stratum. (C) The percentage of patients in the intensive care unit stratum (n=2138) referred from another hospital, per country. (D) Percentage of patients with severe TBI (n=958) with ICP monitoring, per country. These analyses were adjusted for baseline characteristics and stratum and might reflect true differences in policy. TBI=traumatic brain injury. ICU=intensive care unit. ICP=intracranial pressure.

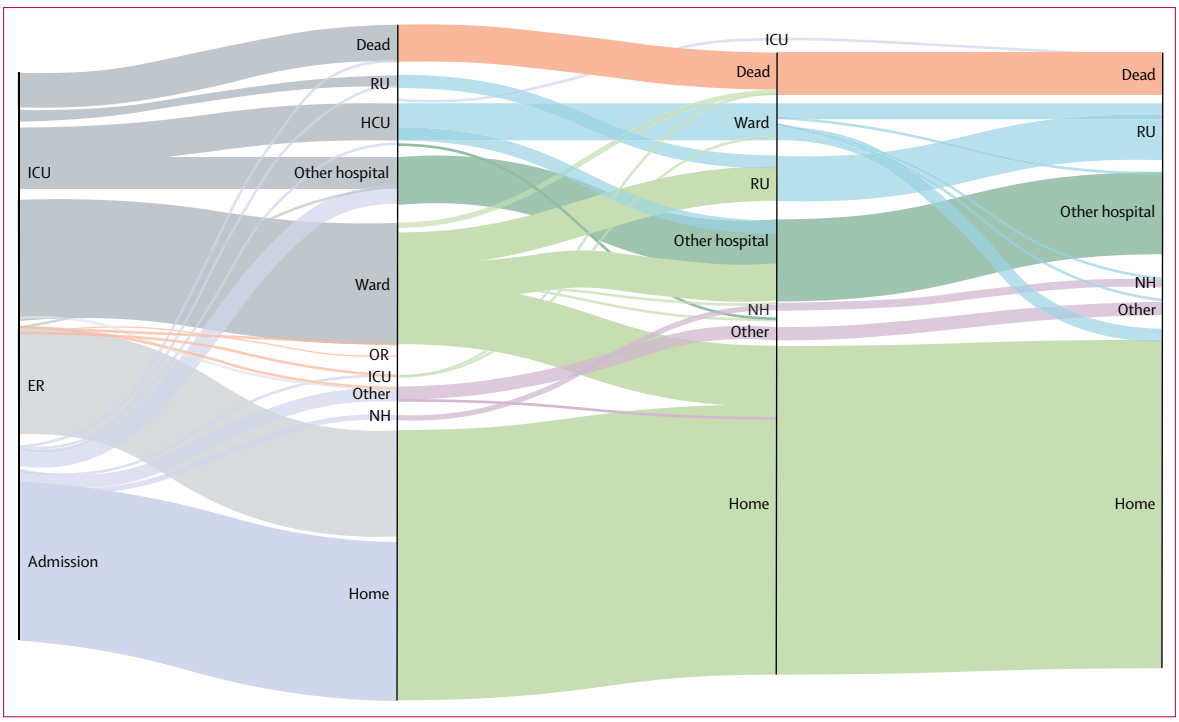

Figure 3: **Care pathway by stratum in the CENTER-TBI core study (n=4509 patients)**
Vertical lines represent the first, second, and third transition of care. For example, most patients from the ER are discharged home and from the ICU most patients go to the ward. The width of each stream reflects the number of patients in that particular stream. The colours have been chosen to allow for clear visual differentiation between streams but do not carry any other intrinsic information. ER=emergency room. ICU=intensive care unit. ED=emergency department. HCU=high care unit. OR=operation room. RU=rehabilitation unit. NH=nursing home.

CT scanning than did those in the registry admission stratum (appendix p 10). Patients in the core ICU stratum had a lower baseline GCS than did those in the registry ICU stratum (appendix p 10).

Early CT scans showed traumatic intracranial abnormalities in 2434 (60%) of 4037 patients at central review (table 1, appendix p 11). The most frequently reported abnormalities were traumatic subarachnoid haemorrhage, contusion, and acute subdural haematoma (appendix p 11). Overall, comparisons between central review scores and investigator scores showed good agreement for 3922 initial CT scans (κ 0·79 for any abnormality; appendix p 12). However, we found low κ values for traumatic axonal injury (0·35) and cisternal compression (0·54; appendix p 12). An early MRI (<3 weeks) showed traumatic intracranial abnormalities in 312 (62%) of 504 patients (table 1). Abnormalities on MRI were found in 60 (30%) of 202 patients with a normal admission CT scan (appendix p 13). Conversely, MRI was normal in 32 (18%) of 182 patients with traumatic abnormalities on the CT scan obtained at presentation. MRI showed more contusions and traumatic axonal injuries than did CT, but CT detected more subarachnoid haemorrhage and epidural haematoma (appendix p 13).

The CENTER-TBI biobank included serum samples from 3833 patients, whole-blood samples from 3649 patients and plasma samples for haemostasis analyses from 604 patients. Values for S100B, NSE, GFAP, NFL, total tau, and UCHL1 were all highest in the ICU stratum (table 1). Concentrations of biomarkers were significantly associated with the presence of intracranial injuries at CT scans (appendix p 23) and scaled inversely with the GCS (appendix pp 24, 25). The concentrations of different biomarkers showed close correlations (appendix p 25).

731 (16%) patients were transferred from another hospital to the study centre, with substantial variations in secondary referral rates across countries (table 2, figure 2). Most secondary transfers occurred in the ICU stratum (table 2). Secondary referral was associated with a five -times increase in time required to reach definitive treatment at the study centre (median 65 min [IQR 45–100] *vs* 297 min [211–440]; p<0·001). 591 (62%) patients with a GCS less than 9 received an intracranial pressure monitor (table 2), but there were substantial variations across countries (figure 2). Intracranial surgery was done in 885 (24%) patients and extracranial surgery in 735 (20%) patients (table 2, appendix p 14). An acute subdural haematoma was the most frequent indication for intracranial surgery (n=323; 25% of all intracranial procedures), and an extremity fracture for extracranial surgery (n=457; 35% of all extracranial procedures). Decompressive craniectomy was done in 204 patients (appendix p 14).

	Overall	ER stratum	Admission stratum	ICU stratum	p value*
In-hospital mortality	363/4471 (8·1%)	3/841 (0·4%)	42/1517 (2·8%)	318/2113 (15·0%)	<0·0001
6-month mortality	473/3804 (12·4%)	9/694 (1·3%)	70/1264 (5·5%)	394/1846 (21·3%)	<0·0001
6-month GOSE	3804/4509 (84·4%)	694/848 (81·8%)	1264/1523 (83·0%)	1846/2138 (86·3%)	..
6-month GOSE <8	2419/3804 (63·6%)	207/694 (29·8%)	665/1264 (52·6%)	1547/1846 (83·8%)	<0·0001
6-month unfavourable outcome (GOSE <5)	966/3804 (25·4%)	31/694 (4·5%)	140/1264 (11·1%)	795/1846 (43·1%)	<0·0001
6-month SF-12v2 mental component summary 9 (n=2300)	50 (41–57)	51 (43–57)	51 (42–57)	48 (39–55)	<0·0001
6-month SF-12v2 physical component summary (n=2300)	48 (39–55)	51 (41–56)	50 (40–56)	46 (36–53)	<0·0001
6-month Qolibri-OS (n=2323)	71 (54–83)	75 (58–91)	75 (58–83)	67 (50–83)	<0·0001
6-month SF-12v2 mental component summary <40 (impaired)	551/2300 (24·0%)	101/480 (21·0%)	184/857 (21·5%)	266/963 (27·6%)	0·002
6-month SF-12v2 physical component summary <40 (impaired)	661/2300 (28·7%)	112/480 (23·3%)	207/857 (24·2%)	342/963 (35·5%)	<0·0001
6-month Qolibri-OS <52 (impaired)	511/2323 (22·0%)	91/474 (19·2%)	160/866 (18·5%)	260/983 (26·4%)	<0·0001

Data are n/N (%) or median (IQR), unless otherwise indicated. ER=emergency room. ICU=intensive care unit. GOSE=Glasgow Outcome Scale Extended. SF-12v2=12-item short form health survey. Qolibri-OS=quality of life after brain injury overall scale. *p values were derived from ANOVA for continuous characteristics and χ^2 statistics for categorical characteristics, comparing strata. The p value assessed compatibility with the null hypothesis of no differences between strata.

Table 3: **Outcomes of patients enrolled in the CENTER-TBI core study**

Only 37 (5%) patients who were initially enrolled in the ER stratum were admitted to hospital (figure 3). Most patients in the ER stratum could be discharged home (table 2). In the admission stratum, most patients went home after a median hospital stay of 2·0 days (IQR 1·0–5·0), and 58 (4%) were discharged directly to a rehabilitation centre (table 2). In the ICU stratum, ICU mortality was 13% (n=272) and most patients were initially discharged to the ward, with a median ICU length of stay of 5·9 days (1·8–15·0) and a total inpatient length of stay of 13 days (5·0–29·0). 518 (27%) patients were subsequently transferred to another hospital, 422 (22%) were further treated at a rehabilitation centre, and 46 (2%) few went to a nursing home (table 2, figure 3).

Three (0·3%) patients in the ER and 42 (2·8%) in the admission strata died. The in-hospital and 6-month mortality in the ICU stratum was much higher (table 3). A 6-month GOSE score was available for 3804 (84%) patients (table 3, figure 4). Death or severe disability occurred in 795 (43%) patients in the ICU stratum. A GOSE less than 8 was observed in 1547 (84%) patients in the ICU stratum, in 665 (53%) in the admission stratum, and in 207 (30%) in the ER stratum (table 3). This failure to achieve a complete functional recovery was also reflected in quality of life scores. 227 (26%) patients in the ICU stratum, 160 (18%) in the admission stratum, and 91 (19%) in the ER stratum had Qolibri-OS scores of less than 52. SF-12v2 scores showed similar results (table 3). Patients with missing outcomes were generally younger, less educated, and less severely injured (appendix p 15).

All covariates for the IMPACT core model and GOSE were available in 1132 (84%) patients older than 14 years with moderate or severe TBI (GCS ≤12). The 6-month mortality was 347 (30%), and 504 (43%) deaths were

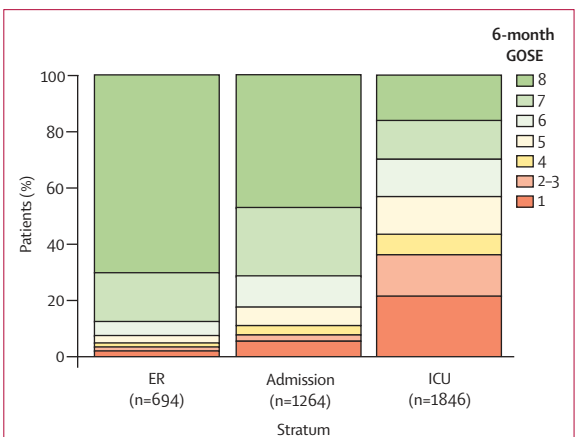

Figure 4: **GOSE at 6 months by stratum in the Center-TBI core study**
GOSE 1=dead. GOSE 8=upper good recovery. GOSE categories 2 (vegetative) and 3 (lower severe disability) are combined because differentiation is not possible for assessments done by postal questionnaire. GOSE=Glasgow Outcome Scale Extended. ER=emergency room. ICU=intensive care unit.

expected (observed to expected ratio 0·70, 95% CI 0·62–0·76). An unfavourable outcome (dichotomised at GOSE <5) was seen in 623 (55%) patients, which was not better than expected (1·07, 0·97–1·14).

Discussion

This integrated analysis describes the landscape of TBI in the CENTER-TBI cohorts who presented in European hospitals, which differs substantially from previous observational studies.[18,19] Patients analysed in these cohorts were older, had more comorbidities, and injuries were most frequently caused by falls. The stratification of patients by care pathway showed clear discordances with

the GCS-based classification of TBI severity, reflects the care that is provided, and sets a context for comparative effectiveness research. CENTER-TBI highlights the substantial burden and poor outcomes of TBI, particularly for patients with mild TBI. A quarter of patients in the core ER stratum and half in the core admission stratum were not fully recovered at 6 months.

Our study suggests that TBI should no longer be considered predominantly a disease of otherwise healthy young male patients.[20] 28% of the population was older than 65 years, compared with around 10% in previous studies.[21] The most common cause of injury was incidental falls, which increased with age, from around 50% in patients aged 50–60 years to more than 75% in patients older than 80 years. These findings motivate an increased focus on fall prevention in older people. The findings also make a strong case for targeting health-care provision and research for TBI in this population, who have been underserved in the past.[22] Clinical trials generally impose age limits (eg, 65 years) and older patients are consequently disenfranchised from research to improve their outcomes. Including older patients in clinical trials, however, produces additional challenges because of comorbidities, age-related neurocognitive changes, and limited neuropsychiatric metrics.[23]

Comorbidities were present in 43% of the population and anticoagulants or platelet aggregation inhibitors were taken by 18%. The highest proportion of previous anticoagulant or antiplatelet therapy was in the admission stratum and might have predicated the need for a period of observation, and driven hospital admission in a substantial subset of patients. Improved prediction of the risks of late lesion development or progression in these patients might avoid unnecessary admission and bring hospital savings.

Alcohol was thought to be a contributory factor in a quarter of cases; recreational and prescription drug use were contributory factors in 6%, broadly in keeping with previous reports.[24–26] Alcohol was highly prominent in violence-related TBI and was involved about twice as often in incidental falls compared with road-traffic incidents. In public health terms, these findings highlight the need for continued efforts to reduce the role of alcohol in injury causation (with an increased focus on fall prevention), while being vigilant about the effects of recreational and prescription drugs.

Conventional characterisation of patients with TBI has relied on the GCS and broad categorisation of structural damage.[27] Our data go beyond these approaches to advance precision medicine in TBI, through detailed structured reporting of CT imaging, the inclusion of MRI, and measurement of blood biomarkers. The structured CT reporting based on the Common Data Elements that we used might be too detailed for routine clinical practice, but could be modified for wider clinical use—eg, by implementing automated pipelines.[28] We showed that MRI in a multicentre international study can be achieved by use of phantoms and healthy controls.[29] MRI detected abnormalities in 30% of CT-negative patients (typically traumatic axonal injury or contusions), and frequently showed more extensive damage in patients who did show CT abnormalities, in keeping with previous reports.[30,31] However, MRI abnormalities were absent in 18% of CT-positive patients, most often in those with traumatic subarachnoid haemorrhage or epidural haematoma. Understanding whether this discordance is due to resolution of abnormalities on later (around 2 weeks) MRI studies, or due to the inherent greater sensitivity of CT for such lesions is crucial, because doing so will inform whether MRI can be safely used as a sole imaging modality in the hyperacute stage after TBI.

We found that biomarker concentrations scaled with the presence of intracranial abnormalities, TBI severity (as defined by GCS), and management pathway (defined by stratum). Our data are concordant with previous reports[32–34] and motivate further research on the role of biomarkers in identifying the need for CT in the patients with least severe injury, selecting CT-negative patients for MRI, and prognostication in all severities of TBI.

We found substantial discordances between conventional stratification of TBI severity (mild, moderate, severe) and care pathways. Patients with mild TBI (GCS >12) constituted a third of patients in the ICU stratum. Plausible explanations for these ICU admissions include advanced age, frailty, comorbidities, increased risks of lesion progression due to use of anticoagulants and antiplatelet drugs, and the need for (extracranial) surgery.[35]

We found substantial differences between countries in pre-hospital care and treatment policies, which support the findings of the provider profiling questionnaires.[5–10] These analyses were adjusted for baseline characteristics and stratum and might reflect true differences in policy. Secondary referrals were associated with substantial delays in access to definitive care, which could drive differences in outcomes between countries.[36] These differences—and the substantial between-country differences we found in the use of intracranial pressure monitoring, cranial and extracranial surgery, and ICU and hospital length of stay—represent opportunities to use comparative effectiveness research to identify best practices.

Although patients with moderate-to-severe TBI in the ICU stratum showed a greater survival than was expected, nearly half had unfavourable outcomes and their functional outcomes were no better than were expected by established prognostic schemes. In the ER stratum, 25% of patients had a GOSE less than 8, and hence had not returned to their pre-TBI baseline functioning by 6 months. These functional deficits were also reflected in quality-of-life measures, and impaired Qolibri-OS and SF-12v2 summary scores were seen in about a quarter.[15] These data are sobering and underline the substantial burden of morbidity for patients who are discharged from ERs, often without follow up, and with no therapeutic options.[37] The lower-than-expected mortality in

combination with unchanged risk of unfavourable outcomes implies that the number of people living with severe disability from TBI has increased.

Despite broad similarities, we found some differences in terms of case-mix between the core study and registry. Some of these differences were expected because recruitment to the core study excluded patients with pre-existing neurological disorders, which could have confounded outcome assessment. The most notable difference was the lower percentage of patients in the ER stratum in the core study compared with those in the registry. This difference probably reflects research interests of participating centres, which are more focussed on more severe injuries, and on the logistic challenges of obtaining informed consent in an environment conditioned towards a high turnover rate. Analyses of the core data can be misleading because of the non-representative distribution across strata. Moreover, some differences were found within strata (eg, with respect to age, injury characteristics, and clinical characteristics at presentation). Caution is therefore appropriate when interpreting the generalisability of the core study results. Also, the stratum-specific results from the core study can only be generalised to patients without pre-existing major cognitive dysfunction.

Strengths of CENTER-TBI are the complementary nature of the core study and the registry, the broad pan-European perspective, the inclusion of all TBI severities and age groups, the focus on care pathways, the detailed clinical characterisation of patients, and establishment of large neuroimaging and biospecimen repositories. Collaboration within the InTBIR initiative will facilitate comparisons with contemporary cohorts and enable meta-analyses for research questions that require larger numbers (eg, genomics). Appropriate interpretation of the findings from CENTER-TBI requires an accurate understanding of the data and their context.

Several limitations should be acknowledged. We focused only on patients presenting to study hospitals and did not include pre-hospital deaths or patients who were not seen in the hospital setting. Second, recruitment to the core study was not consecutive and was determined by site logistics and research interests, meaning that selection bias is possible. Third, participating institutions were mainly referral centres for neurotrauma and results might not be generalisable to other hospital settings. Fourth, in some countries only one centre participated and consequently, potential intra-country health and healthcare disparities (eg, north–south gradients) cannot be assessed. Fifth, the paediatric population was underrepresented because participating centres focused mainly on care for adults. Sixth, not all data elements were complete. In many of the ongoing analyses, multiple imputation will be done for efficient statistical analyses.[38] Similarly, follow-up in the analysis cohort was not complete, although the availability of GOSE outcomes for 84% of the enrolled patients compares favourably with other observational studies.

CENTER-TBI provides detailed insights into the contemporary landscape of TBI in Europe. The results suggest that TBI might no longer be considered predominantly a disease of otherwise healthy young men. Mild TBI not only poses a great societal burden to health care, but also affects functional recovery and quality of life in individuals more than is commonly thought. Substantial geographical differences in care pathways and treatment approaches exist, which provide a basis for comparative effectiveness research to establish best practices. The detailed characterisation of patients in the core study, in combination with the neuroimaging repository and CENTER biobank, will contribute to the development of multidimensional classifications of initial injury severity and outcomes, and to precision medicine approaches. These insights could also provide a basis for re-engaging industry in partnerships for developing new diagnostics and therapeutic interventions for TBI.

Contributors

All authors certify that they have participated in the concept, design, analysis, writing, or revision of the manuscript. All authors participated in the reported analyses and interpretation of results relevant to their domain of interest. EWS, AIRM, and DKM prepared the draft manuscript and coordinated its finalisation. EW and CS did the data extraction, statistical analyses, and drafting of tables and figures. VDK supervised data extraction and drafted figure 1. ThvdV and JV did the structured reporting and analyses of neuroimages. All authors approved the final manuscript.

Declaration of interests

DKM reports grants from the UK National Institute for Health Research, during the conduct of the study; grants, personal fees, and non-financial support from GlaxoSmithKline; personal fees from Neurotrauma Sciences, Lantmaanen AB, Pressura, and Pfizer, outside of the submitted work. AIRM declares consulting fees from PresSura Neuro, Integra Life Sciences, and NeuroTrauma Sciences. GM reports grants from the US National Institute of Neurological Disorders and Stroke and the US Department of Defense, during the conduct of the study. WP reports grants from the Netherlands Brain Foundation. ES reports personal fees from Springer, during the conduct of the study. NvS reports grants from the European Union, during the conduct of the study. All other authors declare no competing interests.

Data sharing

Individual participant data, including data dictionary, and the study protocol, analytical code, and analysis scripts will be available immediately following publication, conditional to approved study proposal, with no end date. Data will be available to researchers who provide a methodologically sound study proposal that is approved by the management committee to achieve the aims in the approved proposal. Proposals can be submitted online at https://www.center-tbi.eu/data. A data access agreement is required and all access must comply with regulatory restrictions imposed on the original study.

Acknowledgments

CENTER-TBI was supported by the European Union 7th Framework programme (EC grant 602150). Additional funding was obtained from the Hannelore Kohl Stiftung (Germany), from OneMind (USA), and from Integra LifeSciences Corporation (USA). We gratefully acknowledge interactions and support from the InTBIR funders and investigators. We are grateful to our patients with TBI for helping us in our efforts to improve care and outcome for TBI.

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