The contemporary landscape of traumatic brain injury in Europe: Case-mix, care pathways, and outcomes from the CENTER-TBI study

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Research in Context

Evidence before this study

In November 2017, the Lancet Neurology Commission on Traumatic Brain Injury (TBI) highlighted existing deficiencies in epidemiology, patient characterization, identifying best practice, outcome assessment, and evidence generation. The Commission concluded that "Concerted efforts are urgently needed to address deficiencies in prevention, care and research", and made a recommendation for large collaborative studies which could provide the framework for precision medicine and comparative effectiveness research (CER).

Added value of this study

The CENTER-TBI Registry and Core Study provide detailed insights into the contemporary landscape of TBI in Europe and constitute a unique resource for improving characterization, developing precision medicine approaches and identification of best practices. The epidemiology of TBI presenting to European centres is changing: patients are older, have most commonly been injured by a fall, and many have 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, have suffered a so-called "mild TBI". However, nearly one third of those discharged from the ER and over half of those admitted to hospital ward did not attain full recovery. There are substantial national and regional variations in care pathways and clinical management.

Implications of all the available evidence:

TBI should no longer be considered predominantly a disease of otherwise healthy young adult males. Falls are the most common cause of TBI and motivate an increased focus for prevention. Mild TBI not only poses the greatest societal burden to health care, but also impacts functional recovery and quality of life in individuals more than commonly thought. Better 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 CER to identify best practice.

Abstract

Background
Traumatic Brain Injury (TBI) poses a large public health and societal problem, but the contemporary landscape in Europe is poorly defined. We aimed to characterize patient case-mix, care pathways, and outcome of TBI.

Methods
CENTER-TBI is a Europe-based observational cohort study, consisting of a Core study (Inclusion criteria: clinical diagnosis of TBI, presentation <24 hours post-injury and indication for computed tomography) and a Registry. Patients were differentiated by care pathway: ER stratum (discharged from emergency room), Admission stratum (hospital ward), and ICU stratum (admission to the intensive care unit). Neuro-images and biospecimens were stored in repositories and outcome assessed 6 months post-injury.

Findings
Data of 4509 patients from 18 countries were analysed in the Core study and 22,782 in the Registry. In the Core study, 848 (19%), 1523 (34%), and 2138 (47%), were in ER, Admission, and ICU strata, respectively. In the ICU stratum, 36% of patients had mild TBI (Glasgow Coma Score 13-15). Compared to the Core cohort, the Registry had more patients in ER (43%) and Admission (38%) strata, with >95% classified as mild TBI. Patients in the Core cohort were older than past studies (median age 50 [IQR: 30-66] years, 28% >65 years), 11% had serious comorbidities, 18% were taking anticoagulant or antiplatelet medication, and alcohol was contributory in 25%. Magnetic resonance imaging (MRI) and blood biomarker measurement enhanced characterisation of injury severity and type. Preliminary MR analyses showed abnormalities in 60 (30%) of 202 patients with normal CT scans. Substantial inter-country differences existed in care pathways and practice. Incomplete recovery (Glasgow Outcome Scale Extended [GOSE] <8) was found in 30%, 53%, and 84% of patients in the ER, Admission and ICU strata respectively. In ICU patients with moderate to severe TBI, the rate of unfavourable outcome (GOSE<5) was 55%, similar to that predicted by the IMPACT prognostic model (O/E ratio 1·06 [95% CI 0·97-1·14]), but mortality was lower than expected (O/E ratio 0·70 [95% CI 0·62-0·76]).

Interpretation
Compared to past studies, many patients with TBI currently presenting to European centres are older and have comorbidities. Overall, patients most commonly present with mild TBI, and often experience incomplete recovery. Precision medicine and identification of best practices with comparative effectiveness research hold promise to improve these outcomes.

Key Words: Traumatic Brain Injury, biomarkers, comparative effectiveness research, epidemiology, neuro-imaging, outcome, precision medicine, prospective observational study

Introduction

Traumatic Brain Injury (TBI) is widely recognized 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 current landscape of TBI in European hospitals is poorly characterized. In 2017, a Lancet Neurology Commission on TBI highlighted the burden posed by TBI to patients, relatives, and society, and provided recommendations to improve patient outcomes through better prevention, clinical care, and research.[2] One recommendation was for large collaborative observational studies to collect longitudinal data, which could inform improved patient characterization to allow better targeting of therapies, and identify best practices through comparative effectiveness research (CER).

The CENTER-TBI project (Collaborative European NeuroTrauma Effectiveness Research: www.center-tbi.eu) is a collaborative European study, conducted within the InTBIR Initiative (https://intbir.nih.gov/),[3] that was designed to address these needs.[4] It includes a multicentre, longitudinal, prospective, observational cohort study (Core study) with highly granular data collection and a Registry, collecting basic administrative data. The main aims are to 1) better characterize Traumatic Brain Injury (TBI) as a disease and describe it in a European context, and 2) identify the most effective clinical interventions for managing TBI. Provider Profiles of participating centres were established to characterize structures and processes of care in preparation for comparative effectiveness research.[5-10] We here aim to describe the contemporary landscape of TBI in Europe, with a focus on the patient case-mix, care pathways, and outcome in the Core study, and to explore generalizability by comparison to the Registry.

Methods

Study design

CENTER-TBI includes a Core study (clinicaltrials.gov NCT02210221) and a Registry (RRID: SCR_015582).[4] Of 92 candidate centres, 65 initiated patient enrolment (Figure 1). The Core study is a prospective observational longitudinal cohort study on patients of all severities of TBI, presenting between December 19, 2014 and December 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 hours of injury, and informed consent obtained according to local and national requirements.[4] The only exclusion criterion was severe pre-existing neurological disorder that could confound outcome assessments. Patients were differentiated by care path into three strata:

1. ER stratum (patients evaluated in the emergency room (ER) and discharged);
2. Admission stratum (admitted to hospital ward);
3. ICU stratum (primary admission to the intensive care unit).

The assignment to a stratum was prospective in the Core study, and retrospective in the Registry. Generalizability 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, time window during the recruitment period of the Core study.

Informed Consent and data de-identification

Consent procedures adhered to local and national requirements. Informed consent was preferred, but seldom possible as most patients were rendered mentally incapacitated by their TBI. Efforts were made to identify a legally acceptable representative (e.g. consultee/proxy). Other options included deferred consent and waiver of consent. We specifically sought consent for blood sampling, DNA analyses, and sharing data with other researchers (both within and outside of Europe). Subjects were free to withdraw, or to be withdrawn by their consultee/proxy: options included complete withdrawal (deletion of all data and destruction of biosamples) and partial withdrawal (cessation of new data accrual, but permission to use data and biosamples already collected). Locally collected data were de-identified and patients allocated a randomly generated GUPI (Global Unique Patient Identifier). All date and time entries were zeroed to the Unix epoch, thus permitting analysis of time intervals while preserving de-identification. Potential patient identifiers were removed from free text, both manually and by automated procedures. Images were defaced upon upload.

Core clinical data

Detailed clinical data were collected using a web-based electronic case report form (eCRF), with stratum-specific work flows (QuesGen Systems Incorporated, Burlingame, CA, USA). These included pre-injury factors, injury details, pre-hospital care, hospital laboratory results, clinical care, post-acute care, and outcome. Variables were coded in accordance with the Common Data Elements (CDE) scheme established by the National Institutes of Health - National Institute of Neurological Disorders and Stroke (NIH-NINDS; https://commondataelements.ninds.nih.gov/). Blood samples and images were obtained according to protocol.[4]

Biobank

The CENTER-TBI biobank (Pecs, Hungary) stored samples of whole blood, serum and plasma for genetic, biomarker and haemostasis analyses, respectively, for both the current study and legacy research.[4] Biomarker analysis was staged: we report on admission samples from 961 patients to explore the potential utility of candidate biomarkers, which included Neuron Specific Enolase (NSE), S-100B , Neurofilament light (NF-L), total tau, glial fibrillary acidic protein (GFAP), and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1).

Neuro-imaging repository

CT scans were obtained in all patients upon presentation. Follow up CT scans were acquired as clinically indicated or by local protocol.[4] MR scans were obtained in a subset of participating centres, and results

are provided on analysis of the first 504 early (<3 weeks) studies. Images were scored locally, details captured in the e-CRF, and subsequently uploaded into a central repository coordinated and maintained by Icometrix (https://icometrix.com/). All uploaded images were read centrally using NINDS CDE-based structured qualitative reporting (https://www.commondataelements.ninds.nih.gov/Doc/SharedForms/F0328_Imaging.docx).

Outcome data

Outcome assessments included health-related quality of life, psychosocial and symptom questionnaires and neuropsychological testing. Questionnaires were translated into national languages and linguistically validated.[4] Telephone or postal interviews were permitted in addition to face-to-face assessments. Cross-sectional outcome assessments across all strata were performed at 6 months post-injury. We report on the three primary outcome measures as defined on registration of the study (functional outcome: GOSE;[11] and health-related quality of life: Qolibri-OS[12] and SF-12v2),[13] and on mortality at 6 months after injury. We classified Qolibri-OS scores <52 and SF-12v2 summary scores < 40 as impaired.[14]

Data handling and curation

Data were stored on a secure database, hosted by the International Neuroinformatics Coordinating Facility (INCF; www.incf.org) in Stockholm, Sweden. Source data verification of major characteristics was undertaken on a quasi-random sample of 1298 patients (28%) by a designated Contract Research Organization (ICON, Ltd, Paris). A multidisciplinary data curation task force addressed data missingness and plausibility, tested for multivariate consistency by cross-checking variables, and calculated derived variables to aid analyses. The cleaned and fully de-identified database was accompanied by a data dictionary with detailed descriptions of data manipulation or transformation applied, and an explicit record of non-resolvable curation issues. A data management tool, 'Neurobot' (http://neurobot.incf.org) was developed by INCF (RRID: SCR_01700). This facilitated data extractions, with the script storable as a unified resource locator for subsequent reuse, reference, or sharing. Imaging files and high-resolution data were stored in separate repositories.[15]

Data analysis

For the current analysis we used Neurobot vs 1.1 (data freeze: January 2019). We report median and interquartile ranges (IQR) for continuous or ordinal variables, and numbers and percentages for categorical variables. All analyses were differentiated by stratum and performed in R statistical software (3.5.1) and RStudio (1.0.136). Analysis of variance (ANOVA) was used for comparison of continuous variables across strata. The chi-square test was used for comparison of categorical variables. Kappa statistics were used to express the agreement between central and local radiological evaluation of admission CT scans and for CT versus MR scans.

Patients without any GOSE assessment were excluded from analysis (n=705; 16%). The 6-month GOSE scores were available within the 5-8 month protocol window for 2186 (62%) patients. For 988 patients (22%) with scores outside the 5-8 month window, we used a multistate model to impute the 180-day GOSE (msm R package).[16] We used the IMPACT Core model for the expected mortality and proportion with unfavourable GOSE outcome among patients with moderate or severe TBI (Glasgow Coma Score <= 12).[17] Observed mortality and unfavourable GOSE outcomes were compared to expected outcomes and expressed as a ratio with 95% confidence intervals estimated according to a Poisson distribution.
For calculating SF-12v2 summary scores, we used the SF-12v2 questionnaires where completed, supplemented by derived scores using SF-36v2 items when available.

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The funders had no role in the collection, analysis and interpretation of data, nor in the writing of the report or in publication decisions. The authors had full access to study data and the senior authors had final responsibility for the decision to publish.

Results

Data collection
The Core study enrolled 4,559 patients and the Registry 22,849 from 65 sites in 19 countries. Of these, data from 4509 patients in the Core study and 22782 in the Registry were analysed (Figure 1). The median enrolment by centre in the Core Study was 50 patients (IQR: 21-107), with widely different distributions across strata (Figures 2 and S1). In the Core study, 848 (19%), 1523 (34%), and 2138 (47%), were in ER, admission and ICU strata respectively. Compared to the Core study, the Registry enrolled more patients in the ER (9839, 43%) and Admission strata (8571, 38%) (Figure 1).

Baseline and Injury characteristics of Core cohort (Table 1)
Overall, the median age was 50 (IQR: 30–66) years, with 28% >65 years of age. Patients in the Admission stratum were older (53 years, 32% >65), compared to those in the ER and ICU strata. Male patients were overrepresented in every stratum, most notably in the ICU stratum (73%). At higher age, however, the proportion of females was higher in the ER and Admission strata (Figure 3). Mild or severe systemic disease was reported in 43%.

Differences were noted in patient characteristics between the three strata with respect to socio-economic characteristics (education, marital and employment status), medical history (especially frequency of having had a previous TBI), cause of injury and clinical severity (Tables 1, S1 to S4). An incidental fall was the most common cause of injury in the ER and Admission strata (51% in both). A clear association with age was noted, with high rates of falls occurring in those < 10 years of age and in the elderly (>65 years, Figure S2). Road traffic incidents were more common in the ICU stratum (45%). Alcohol use was reported in 64% of all violence-related TBI, in 28% of incidental falls and in 17% of road traffic incidents (Figure S3). Recreational and prescription drug use were reported in 5·7% of patients.

Clinical severity varied by stratum: In the ER and Admission strata, the median baseline Glasgow Coma Score (GCS) was 15 and 99% and 93% respectively were classified as mild TBI (GCS 13-15) (Table 1, Figure 4). In the ICU stratum, the median GCS was 9 and 36% of patients had a GCS>12. Major extracranial injuries (AIS>=3) were reported in 27% of patients in the Admission stratum and in 55% of those in the ICU stratum. The body region most commonly injured was thorax/chest (35%), whilst concomitant serious spinal injuries occurred in 18% (Table S4).

Comparisons with Registry
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 overall comparison between the two cohorts. When differentiated by stratum, patients in the Core study broadly resembled those in the Registry (Table S5): Similar proportions had serious extracranial injuries (27% vs 28% in the admission cohorts, and 55% vs 53% in the ICU cohorts respectively), and similar proportions of patients in the ICU strata arrived intubated at the ER (44% in Core and 41% in Registry) . In the ICU strata, the frequency of emergency surgical procedures was similar (e.g. craniotomy for haematoma/contusion 14 vs 16%, respectively. In-hospital mortality was similar across strata (e.g. 15% and 19% for the ICU stratum in Core and Registry, respectively). Some differences existed in other baseline and injury characteristics (Table S5): Patients in the Core ER stratum were more frequently injured in road traffic incidents (32% vs 24%) and had more intracranial abnormalities on CT scanning (15% vs 5·1%) than their Registry counterparts. Patients in Core admission stratum were younger (53 vs 64 years), more often male (65 vs 60%), more frequently injured in road traffic incidents (33% vs 25%) and had more intracranial abnormalities on CT scanning (49% vs 36%). The Core ICU stratum enrolled patients with a lower baseline GCS (median 9 vs 12, Table S5).

CENTER-TBI Neuro-imaging repository and biobank
Early CT scans showed traumatic intracranial abnormalities in 2434 of 4037 (60%) at central review: 15%, 49%, and 89% in the ER (n=127), admission (n=680) and ICU (n=1627) strata, respectively (Table 1, Table S6). The most frequently reported abnormalities were traumatic subarachnoid haemorrhage (1843, 46%) contusion (1325, 33%) and an acute subdural hematoma (1241, 31%; Table S6).

Comparisons between central review scores and investigator scores showed good agreement for 3922 initial CT scans (kappa 0·79 for any abnormality, Table S7). Relatively low kappa values were found for traumatic axonal injury (0·35) and cisternal compression (0·54). An early MRI (<3 weeks) showed traumatic intracranial abnormalities in 312 of 504 patients (62%; Table 1). Abnormalities on MR were noted in 60/202 (30%) with a normal admission CT scan (Table S8). Conversely, MR imaging was normal in 32/182 (18%) patients with traumatic abnormalities on the CT scan obtained at presentation. MRI showed more contusions (32% vs 22%) and traumatic axonal injuries (35% vs 5%), but CT detected more subarachnoid hemorrhage (32% vs 23%) and epidural hematoma (9% vs 6%, Table S8).

The CENTER-TBI biobank included serum samples from 3833 subjects, whole blood samples from 3649 patients and plasma samples for haemostasis analyses from 604 subjects. Values for S100B, NSE, GFAP, NFL, Total Tau, and UCHL1 were all highest in the ICU stratum (Table 1). Levels of biomarkers were significantly associated with the presence of intracranial injuries at CT scans (Figure S4), and scaled inversely with the GCS (Figure S5). The levels of different biomarkers showed close correlations (Figure S6).

Care pathways

In total, 731 patients (16%) were transferred from another hospital to the study centre, with substantial variations in secondary referral rates across countries (Table 2; Figure 5); most secondary transfers (24%) occurred in the ICU stratum (Table 2). Compared to primary referral, secondary referral increased the time required to reach definitive treatment at the study centre 5 times (median 65 minutes *vs.* 295 minutes; p<0·001). Overall, 591 (62%) patients with a GCS <9 received an ICP monitor (Table 2), but there were substantial variations across countries (Figure 5). Intracranial surgery was performed in 885 (24%), and extracranial surgery in 735 patients (20%, Tables 2 and S9). An acute subdural hematoma 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 performed in 195 patients (Table S9).

Of patients initially enrolled in the ER stratum, 37 (4·8%) were admitted to hospital (Figure 6). Nevertheless, the vast majority of patients in the ER stratum (99%) could be discharged home (Table 2). From the Admission stratum, most patients went home (85%) after a median hospital stay of 2·5 days, and 59 (4%) were discharged directly to a rehabilitation centre. For the ICU stratum, ICU mortality was 13% (n=272), and most patients were initially discharged to the ward (n=1131; 60%), with a median ICU length of stay of 6.1 (IQR: 1·9-15) days, and a total inpatient length of stay of 17 (IQR: 7·9–32) days. A total of 518 (27%) were subsequently transferred to another hospital, some were further treated at a rehabilitation centre (n=421, 22%), few went to a nursing home (n=46, 2·4%) (Table 2, Figure 5).

Outcome

Some patients in the ER and Admission strata died (3, 0·3% and 42, 2·8%, respectively). The in-hospital and 6-month mortality in the ICU stratum was much higher (15% and 21%, Table 3). A 6-month GOSE score was available for 3804 patients (87%, Table 3, Figure 7). Death or severe disability occurred in 43% of patients in the ICU stratum. A GOSE < 8 was observed in 84% of patients in the ICU stratum, in 53% of the Admission stratum, and in 30% of the ER stratum (Table 3). This failure to achieve a complete functional recovery was also reflected in quality of life scores: rates of Qolibri-OS of <52 in survivors were 25%, 18%, and 19% in the ICU, Admission and ER strata, respectively. SF-12v2 scores showed similar results (Table 3). A comparison of baseline characteristics between patients with and without available outcome showed that those with missing outcome were generally younger, less educated, less severely injured and that alcohol was more frequently involved (Table S10).

In 1132 patients >14 years with moderate or severe TBI (GCS <=12), all covariates for the IMPACT core model and GOSE were available (84% of eligible patients). The observed 6-month mortality was 347 (30%), while 504 (43%) deaths were expected (O/E ratio 0·70 [95% CI 0·62-0·76]). An unfavourable outcome (dichotomised at GOSE<5) was noted in 55%, which was not better than expected (O/E ratio 1·07 [95% CI 0·97-1·14]).

Discussion

This integrated analysis of the CENTER-TBI study describes the landscape of TBI as currently seen in European hospitals, which differs substantially from previous observational studies: Patients are older, have more co-morbidities, and injuries are most frequently caused by falls. The median age in the Core Study is 50, substantially higher than in the UK 4 centre study or the EBIC survey.[18-19] CENTER-TBI is unique in that it covers all severities of TBI and differentiates patients by care pathway rather than by the traditional classification of TBI severity by the GCS into mild, moderate or severe. The stratification of patients by care pathway demonstrates clear discordances with GCS-based classification of TBI severity, reflects care provided, affords new clinical insights, and sets a context for comparative effectiveness research (CER). CENTER-TBI highlights the substantial healthcare burden and outcome impact of TBI, particularly for "mild" TBI. Despite a median admission GCS of 15, a quarter of patients in the Core ER stratum and half in the Core Admission stratum were not fully recovered at 6 months. The Registry showed that such patients constitute 81% of all patients presenting with TBI, suggesting that while severe TBI may be devastating for individuals, mild TBI poses the greatest burden to health systems. For some individuals, mild TBI may not be "mild" at all, and results in a greater burden of late problems than commonly appreciated.

TBI epidemiology: A changing landscape

Our study confirms that TBI should no longer be considered predominantly a disease of healthy young males.[20] Overall, 28% of the population was >65 years of age compared to ~10% in past series.[21] The most common cause of injury was incidental falls, which increased with age, from around 50% in the age group 50-60 to over 75% in patients over age 80 years. These findings motivate an increased focus on fall prevention in the elderly.

Co-morbidities were present in 43% of the population, and anticoagulants or platelet aggregation inhibitors taken by 18%, reflecting the increasing age and frequent need for treatment of cardiovascular comorbidities. The highest incidence of prior anticoagulant or antiplatelet therapy was in the admission stratum (21%) and may have predicated the need for a period of observation, and driven hospital admission in a substantial subset of patients. Better prediction of the risks of late lesion development or progression in these patients might avoid unnecessary admission and result in health-economic benefits.

Alcohol was thought to be a contributory factor in a quarter of cases; recreational and prescription drug use were contributory factors in 6%.These numbers are broadly in keeping with recent reports.[22-24] Alcohol was highly prominent in violence-related TBI and involved about twice as often in incidental falls compared to RTIs. In public health terms, these findings speak to 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 impact of recreational and prescription drugs.

Towards precision medicine approaches

Conventional characterization of patients with TBI has relied on the GCS and broad categorisation of structural damage.[25] 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 CENTER-TBI neuro-imaging repository and biobank are likely the largest in the world on TBI. The NINDS CDE-based structured CT reporting used may be too detailed for routine clinical practice, but identification of its essential elements could allow for wider clinical use. We are exploring automated pipelines to provide consistent, objective and accurate detection and quantification of imaging covariates,[26] which have prognostic relevance and could allow better patient stratification. Implementation of harmonized MR imaging in a multicentre international study which included non-research imaging centres was demanding, as scanners and software differ and units for standardization are lacking. We used phantoms and healthy controls to develop harmonized sequences across vendors and machines.[27] Our preliminary results show that MRI detected

abnormalities in 30% of CT negative patients (typically traumatic axonal injury or contusions), and frequently uncovered more extensive damage in patients who did show CT abnormalities. The increased sensitivity of MRI in this regard (particularly for TAI) is in keeping with past reports.[28,29] However, we also found that MR abnormalities were absent in 18% of CT positive patients, most often with tSAH or epidural haematoma. This may be because later (~2 week) MRI studies may miss initial lesions that resolve,[30] or because CT is inherently more sensitive at detecting some types of injury. Determining which of these factors is responsible for CT positive-MRI negative imaging is critical, since it will inform whether MRI can be safely used as a sole imaging modality in the hyperacute stage after TBI. CENTER-TBI has promoted the collection of MRI data within 72 hours of injury in a subset of patients, and analyses of this subgroup will permit better quantification of the complementary diagnostic and prognostic information provided by these imaging techniques.

We found that biomarker levels scaled with the presence of intracranial abnormalities, TBI severity (as defined by GCS), and management path (defined by stratum). Our data are concordant with recent reports,[31,32] 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.

Care pathways and country/centre differences

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 admissions to the ICU include advanced age, frailty, comorbidities, increased risks of lesion progression due to anticoagulants and antiplatelet agents, the need for surgery, and/or extracranial injury.[33] Indeed, half of patients in the ICU stratum had significant extracranial injury. Ongoing analyses will address the drivers, costs, and benefits of ICU admissions for mild TBI.

We noted significant differences between countries in prehospital care and treatment policies, which confirm the findings of the provider profiling questionnaires.[5-10] Primary and secondary referrals were associated with substantial differences in time to access definitive care, and the differences we observe in secondary referral rates might therefore potentially drive differences in outcomes between countries.[34] These differences, and the substantial between-country differences we demonstrate in use of ICP monitoring, cranial and extracranial surgery, and ICU and hospital length of stay, represent opportunities to use CER to identify best practices.

Outcome

TBI remains a disease with poor outcomes. Though patients with moderate to severe TBI in the ICU stratum showed a greater survival than expected, nearly half experienced unfavourable outcome and their functional outcome was no better than expected. In the ER stratum, 25% of patients had a GOSE <8, and hence had not returned to their pre-TBI baseline functioning by 6 months. These functional deficits are also reflected in quality of life measures, and an impaired Qolibri-OS and SF-12v2 summary scores were seen in 21% (Qolibri-OS), 23% (MCS) and 28% (PCS) respectively of survivors.[14] These data are sobering, and underline the substantial burden of morbidity for subjects who are being discharged from Emergency Rooms, often without follow up, and with no current therapeutic options. There is an urgent need to improve outcomes in all patients with TBI, and not least in those with supposedly mild TBI.

Generalizability

Despite broad similarities, we observed some significant differences in terms of case-mix between the Core study and Registry. Some of these differences were expected, since recruitment to the Core study excluded patients with pre-existing neurological disorders which could have confounded assessment of the outcome impact of TBI. This provided a clear reason why patients in the Registry

(particularly in the Admission stratum) were older and presented more frequently with falls. The most notable difference, however, was the lower percentage of patients in the ER stratum in the Core study (19%) compared to the Registry (43%). This difference likely reflects research interests of participating centres, which are more focussed on more severe injuries, and on the logistic challenges for obtaining informed consent in an environment conditioned towards a high turn-over rate. Some caution is therefore appropriate when interpreting generalizability of the Core study results.

Strengths and limitations

Particular 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 characterization of patients, and establishment of large neuro-imaging and biospecimen repositories. Collaboration within the InTBIR initiative will facilitate meta-analyses across InTBIR studies. It may permit addressing research questions that require larger numbers, such as genetic markers in TBI. Several limitations should be acknowledged. We focused only on patients presenting to study hospitals and did not include pre-hospital deaths or patients not seen in the hospital setting. Second, recruitment to the Core study was not consecutive and determined by site logistics and research interests. Third, participating institutions were mainly referral centres for neurotrauma, and results may not be completely generalizable to all hospital settings. Fourth, we recognize that the paediatric population was under-represented, as participating centres mainly focused on care for adults. Fifth, not all data elements were complete. In many of the ongoing analyses, multiple imputation will be performed for efficient statistical analyses.[35] Similarly, while ongoing efforts are steadily increasing rates of recorded outcomes in the dataset, follow-up in the current analysis cohort was not complete, although the availability of GOSE outcomes for 86% of the enrolled patients compares very favourably to other observational studies. Completion rates of other outcome instruments and neuropsychological testing were somewhat lower.

Conclusions

CENTER-TBI provides detailed insights into the contemporary landscape of TBI in Europe. TBI should no longer be considered predominantly a disease of otherwise healthy young adult males. Mild TBI not only poses the greatest societal burden to health care, but also impacts functional recovery and quality of life in individuals more than commonly thought. Substantial geographic differences in care pathways and treatment approaches exist, which provide a basis for comparative effectiveness research to determine best practices. The detailed characterization of patients in the Core study, in combination with the neuro-imaging repository and CENTER biobank will contribute to the development of multidimensional classifications of initial injury severity and outcome, and to precision medicine approaches.

Acknowledgements
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Authors' statement
All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated in the concept, design, analysis, writing, or revision of the manuscript.

Ethics statement
The CENTER-TBI study (EC grant 602150) 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". Informed Consent by the patients and/or the legal representative/next of kin was obtained, accordingly to the local legislations, for all patients recruited in the Core Dataset of CENTER-TBI and documented in the e-CRF.

Ethical approval was obtained for each recruiting sites. The list of sites, Ethical Committees, approval numbers and approval dates can be found on https://www.center-tbi.eu/project/ethical-approval

Data sharing statement:

Will individual participant data be available? `	Yes, including data dictionary
What other documents will be available?	Study protocol, analytic code and analysis scripts
When will data be available?	Immediately following publication, conditional to approved study proposal; no end date.
With whom?	Researchers who provide a methodologically sound study proposal that is approved by the management committee.
For what type of analyses?	To achieve the aims in the approved proposal
By what mechanism will data be made available?	Proposals may be submitted online 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.

Table 1: Characteristics of 4509 patients enrolled in the CENTER-TBI Core study

Variable	**N complete**	**N (%)**	**ER (N, %)**	**Admission (N, %)**	**ICU (N, %)**	p-value *
Total number of patients		4509	848	1523	2138	
Demographic characteristics						
Age (median (IQR))	4509	50 (30-66)	48 (29-64)	53 (32-69)	49 (29-65)	0·001
• >65 years		1254 (28%)	209 (25%)	493 (32%)	552 (26%)	
Male sex	4509	3022 (67%)	473 (56%)	988 (65%)	1561 (73%)	<0·001
Caucasian	4307	4158 (97%)	810 (97%)	1425 (96%)	1896 (97%)	0·33
Socio-economic characteristics						
Years of education (median (IQR))	3212	13 (10 – 16)	13 (11 – 16)	13 (11 – 16)	12 (10 – 15)	<0·001
Highest level of education	3566					<0·001
• College / University		850 (24%)	236 (30%)	334 (26%)	280 (19%)	
Married/living together	4075	2070 (51%)	385 (48%)	717 (50%)	968 (52%)	0·15
Employment status before injury	3980					0·05
• Working		1946 (49%)	427 (52%)	638 (45%)	881 (50%)	
Pre-injury health status and medical history						
Pre-injury ASA-PS classification	4384					0·56
• A patient with mild systemic disease		1410 (32%)	268 (32%)	507 (34%)	635 (31%)	
• A patient with severe systemic disease		462 (11%)	93 (11%)	159 (11%)	210 (10%)	
Previous TBI	4158	402 (9·7%)	120 (15%)	149 (10%)	133 (7·0%)	<0·001
Anticoagulants	4345	298 (6··9%)	46 (5·5%)	133 (8·8 %)	119 (6·0%)	<0·001
Platelet aggregation inhibitors	4345	474 (11%)	85 (10%)	178 (12%)	211 (11%)	0·38
Cause of injury and use of medication						
Cause of injury	4388					<0·001
• Road traffic incident		1682 (38%)	266 (32%)	490 (33%)	926 (45%)	
• Incidental fall		2024 (46%)	424 (51%)	761 (51%)	839 (41%)	
Alcohol involved in the injury (yes or suspected)	4163	1054 (25%)	137 (17%)	384 (27%)	533 (28%)	<0·001
• Road traffic incident		262 (26%)	25 (19%)	76 (21%)	161 (33%)	<0·001
• Incidental Fall		533 (54%)	72 (55%)	209 (57%)	252 (51%)	<0·001

Clinical presentation						
GCS baseline (median (IQR))	4330	15 (10-15)	15 (15-15)	15 (14-15)	9 (4-14)	<0·001
Mild (13-15)		2955 (68%)	826 (99%)	1409 (93%)	720 (36%)	
Moderate (9-12)		389 (9·0%)	2 (0·2%)	59 (3·9%)	328 (15%)	
Severe (3-8)		986 (23%)	4 (0·5%)	21 (1·4%)	961 (45%)	
Pupillary reactivity	4247					<0·001
• One pupil unreactive		164 (3·9%)	3 (0·4%)	27 (1·9%)	134 (6·6%)	
• Two pupils unreactive		281 (6·6%)	16 (2·0%)	19 (1·3%)	246 (12%)	
Hypoxia (prehospital/ER phase)	4256	299 (7·0%)	3 (0·4%)	30 (2·1%)	266 (13%)	<0·001
Hypotension (prehospital/ER phase)	4296	297 (6·9%)	4 (0·5%)	26 (1·8%)	267 (13%)	<0·001
Any major extracranial injury (AIS >=3)	4509	1642 (36%)	46 (5·4%)	422 (28%)	1174 (55%)	<0·001
CT characteristics						
Any intracranial abnormality at local reading	3947	2271 (58%)	55 (7·0%)	639 (47%)	1577 (87%)	<0·001
Any intracranial abnormality at central reading	4037	2434 (60%)	127 (15%)	680 (49%)	1627 (89%)	<0·001
MR characteristics						
Any intracranial abnormality at central reading	504	312 (62%)	32 (26%)	101 (56%)	179 (91%)	<0·001
Biomarkers[#]						
NSE (median (IQR), ng/ml)	961	18 (13-27)	13 (11-16·8)	14 (11-18)	23 (15-34)	<0·001
S100B (median (IQR), µg/L)	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)	<0·001
GFAP (median (IQR), ng/mL)	1010	4·4 (0·8 – 17)	0·3 (0·1 – 1·0)	1·7 (0·6 – 5·1)	11 (3·4 – 31)	<0·001
NF-L (median (IQR), pg/mL)	1010	23 (10 – 60)	8·3 (5·1 – 15)	16 (8 – 30)	40 (18 – 95)	<0·001
t-Tau (median (IQR), pg/mL)	1010	4 (1·7 – 11)	1·2 (0·8 – 2·0)	2·3 (1·3 – 4·5)	7·9 (3·3 – 17)	<0·001
UCHL1 (median (IQR), pg/mL	1009	127 (48 – 381)	35 (20 – 64)	68 (34 – 122)	275 (109 – 597)	<0·001
Laboratory measurements						
Hemoglobin (median (IQR), g/dL)	3846	14 (12 – 15)	14 (13 – 15)	14 (13 – 15)	13 (12 – 14)	<0·001
Glucose (median (IQR), mmol/L)	3492	6·9 (5·9 – 8·3)	6 (5·3 – 7·1)	6·5 (5·7 – 7·8)	7·3 (6·3 – 8·9)	<0·001

ASA-PS = The American Society of Anesthesiologists (ASA) *physical status classification system,* GCS = Glasgow Coma Scale; S100B = S100 calcium-binding protein B, NSE = Neuron-Specific Enolase, NF-L = Neurofilament Light, GFAP = Glial Fibrillary Acidic Protein, t-Tau = total Tau, UCHL1 = Ubiquitin Carboxy-Terminal Hydrolase L1; [#] NSE and S-100B were measured on the e602 module of a Cobas 8000 analyzer (Roche Diagnostics International Ltd· Rotkreuz, Switzerland) in Pecs, Hungary and NF-L, total Tau, GFAP, and UCH-L1 on the Quanterix SIMOA Neurology 4-plex kit (Quanterix, Lexington, MA, USA), at the University of Florida, USA.

* p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively, comparing strata

Table 2: Care pathways of 4509 patients enrolled in the CENTER-TBI Core study

Variable	N complete	N (%)	ER (N, %)	Admission (N, %)	ICU (N, %)	p-value*
Total number of patients		4509	848	1523	2138	
Referral						
Primary referral	4492	3761 (84%)	818 (97%)	1323 (87%)	1620 (76%)	<0·001
• Time to study center (median (IQR)) – mins	4489	65 (45-101)	62 (42-106)	60 (41-96)	50 (72-101)	
Secondary referral	4492	731 (16%)	29 (3·4%)	199 (13%)	503 (24%)	<0·001
• Time to study center (median (IQR)) – mins	4489	295 (211-438)	257 (151-316)	294 (205-428)	300 (217-445)	
Diagnostic and surgical interventions						
Time from injury to first CT (median (IQR)) – minutes	3927	110 (71-148)	136 (92-201)	105 (74-158)	105 (78-143)	<0·001
ICP monitor placed	2169	924 (43%)	0 (0)	3 (7%)	921 (44%)	<0·001
GCS <= 8	958	591 (62%)	0 (0)	0 (0)	591 (62%)	<0·001
Intracranial surgery	3686	885 (24%)	1 (2·4%)	64 (4·2%)	820 (39%)	<0·001
Extracranial surgery	3685	735 (20%)	1 (2·4%)	128 (8·4%)	606 (29%)	<0·001
Length of stay	3777					
From arrival ER to hospital discharge in hours and days		5·1 (1·3 – 16) days	11 (5·3 – 23) hours	2·5 (1·2 – 5·8) days	17 (7·9 – 32) days	<0·001

Hospital Discharge Destination	4189				<0·001
Home		2645 (63%)	804 (99%)	1246 (85%)	595 (31%)
Rehab Unit		480 (11%)	0 (0·0%)	59 (4·0%)	421 (22%)
Other Hospital		635 (15%)	0 (0·0%)	117 (8·0%)	518 (27%)
Nursing Home		49 (1·2%)	1 (0·1%)	2 (0·1%)	46 (2·4%)
Other		17 (0·4%)	0 (0·0%)	0 (0%)	17 (0·9%)
In-hospital mortality		363 (8·7%)	3 (0·4%)	42 (2·8%)	318 (15%)

ICP = Intracranial Pressure, GCS = Glasgow Coma Scale

* p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively, comparing strata

Table 3: Outcomes of 4509 patients enrolled in the CENTER-TBI Core study

	N complete	All (N, %)	ER (N, %)	Admission (N, %)	ICU (N, %)	p-value*
Total number of patients		4509	848	1523	2138	
In-hospital mortality	4469	363 (8·1%)	3 (0·4%)	42 (2·8%)	318 (15%)	<0·001
6 months mortality	3804	473 (12%)	9 (1·3%)	70 (5·5%)	394 (21%)	<0·001
6 months GOSE – N completed	3804	3804 (84%)	694 (82%)	1264 (83%)	1846 (86%)	
6 months GOSE < 8	3804	2419 (64%)	207 (30%)	665 (53%)	1547 (84%)	<0·001
6 months Unfavourable outcome (GOSE < 5)	3804	966 (25%)	31 (4·5%)	140 (11%)	795 (43%)	<0·001
6 months SF-12v2 Mental Component Summary (median (IQR))	2229	50 (41 – 57)	51 (42 – 57)	51 (42 – 57)	48 (39 –56)	<0·001
6 months SF-12v2 Physical Component Summary (median (IQR))	2229	49 (39 – 55)	51 (41 – 56)	50 (40 – 55)	46 (36 - 53)	<0·001
6 months Qolibri-OS (median (IQR))	2233	71 (54-83)	75 (58-91)	75 (58-83)	71 (52-83)	<0·001
6 months SF-12v2 Mental Component Summary <40 (impaired)	2229	522 (23%)	100 (21%)	181 (21%)	241 (27%)	0.012
6 months SF-12v2 Physical Component Summary <40 (impaired)	2229	630 (28%)	111 (23%)	205 (24%)	314 (35%)	<0·001
6 months Qolibri-OS < 52 (impaired)	2233	474 (21%)	89 (19%)	158 (18%)	227 (25%)	0·002

GOSE = Glasgow Outcome Scale Extended, SF-12v2 = Short-Form 12v2, Qolibri-OS = Qolibri-Overall Scale

* p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively

Figure 1: Centre participation and recruitment to CENTER-TBI Study. The accrual to ER, Admission, and ICU strata was defined prospectively in the Core study, and retrospectively in the Registry.

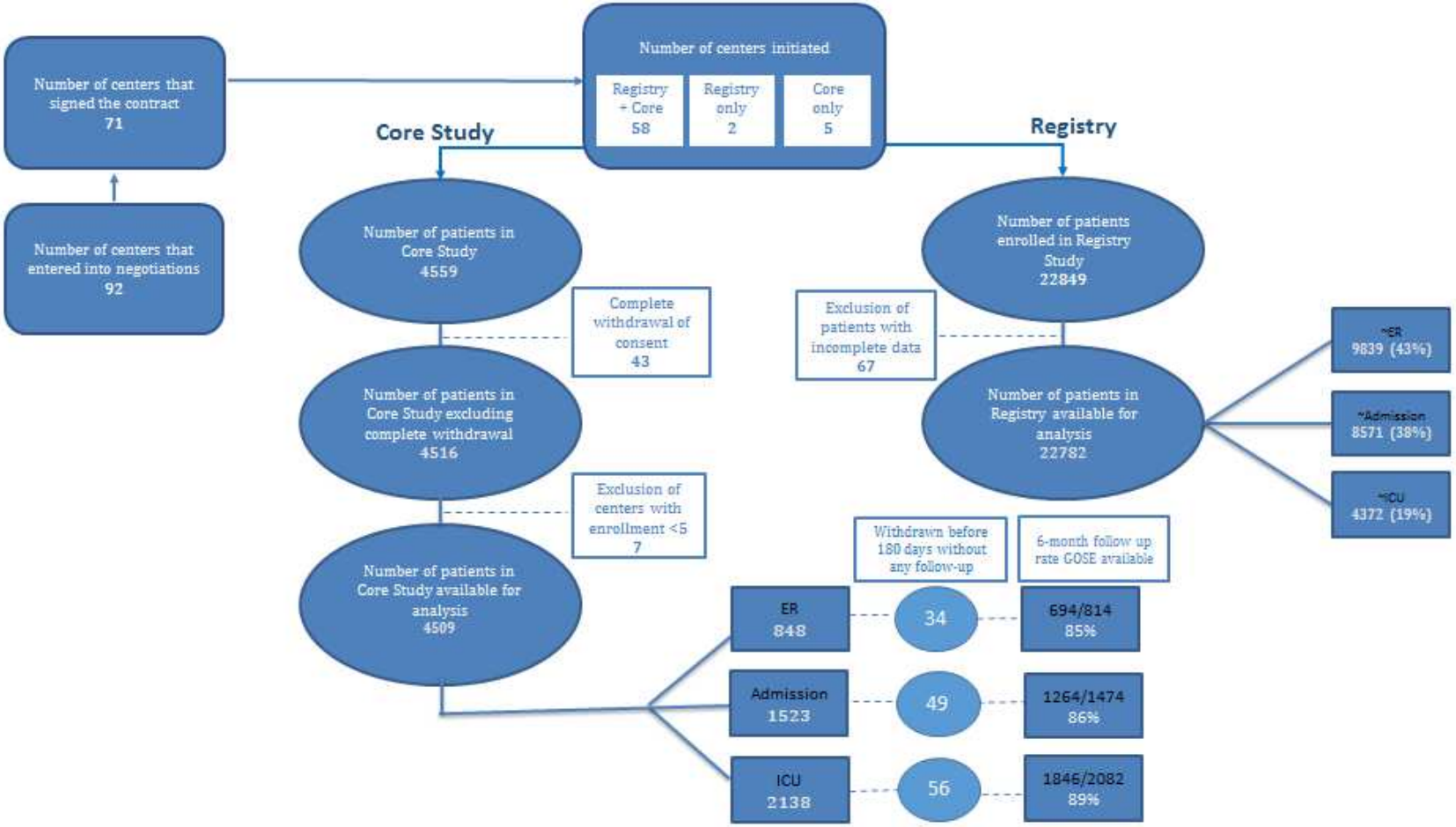
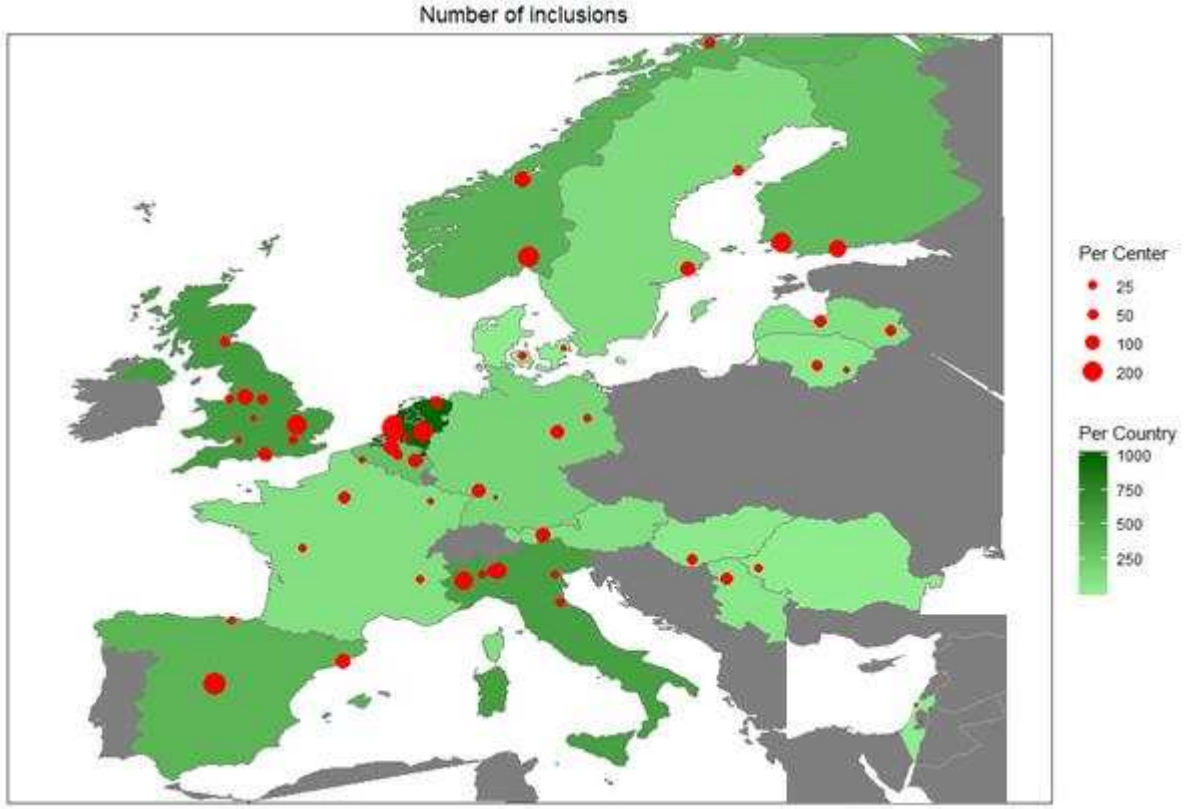


Figure 2: Participation per study centre & country in the Center-TBI Core study (n=4509 patients)



The median enrollment by country was 125 (IQR: 50 – 403) and median by site 50 (IQR: 21 – 107). Four countries accounted for 2563/4509 (57%) of recruited patients (Netherlands: N=7 centres, n=1,006 patients; the UK: N=9 centres, n=578 patients; Italy: N=8 centres, n=560 patients and Norway: N=3 centres, n=419 patients).

Figure 3: Age by sex distribution by stratum in the Center-TBI Core study (n=4509 patients). The ER stratum included most females and the ratio of females to males increased with older ages in each stratum.

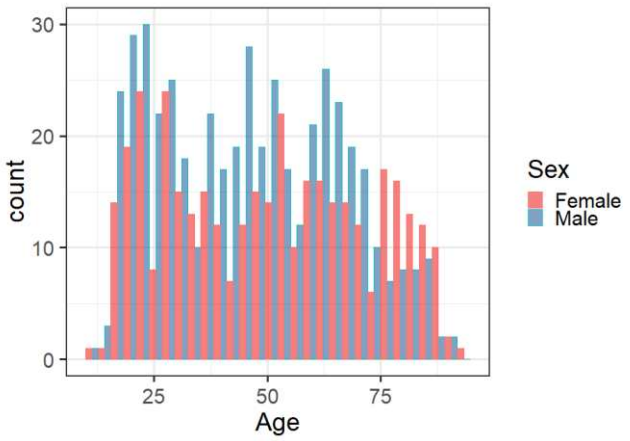
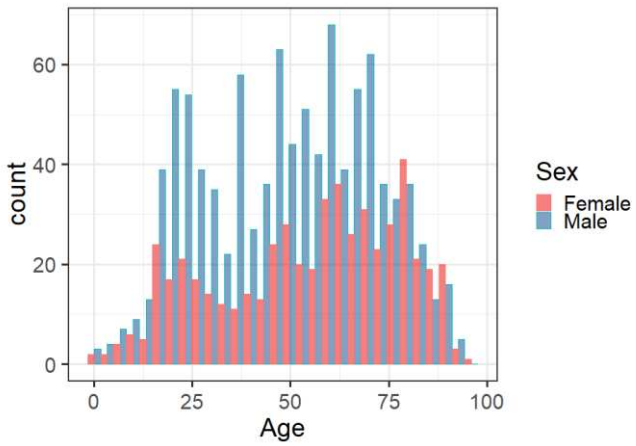
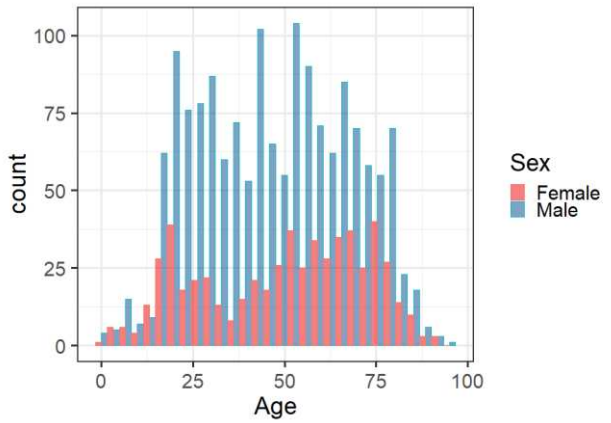
		
ER (n=848)	Admission (n=1523)	ICU (n=2138)

Figure 4: GCS distribution by stratum, CENTER-TBI- core (n=4,344)

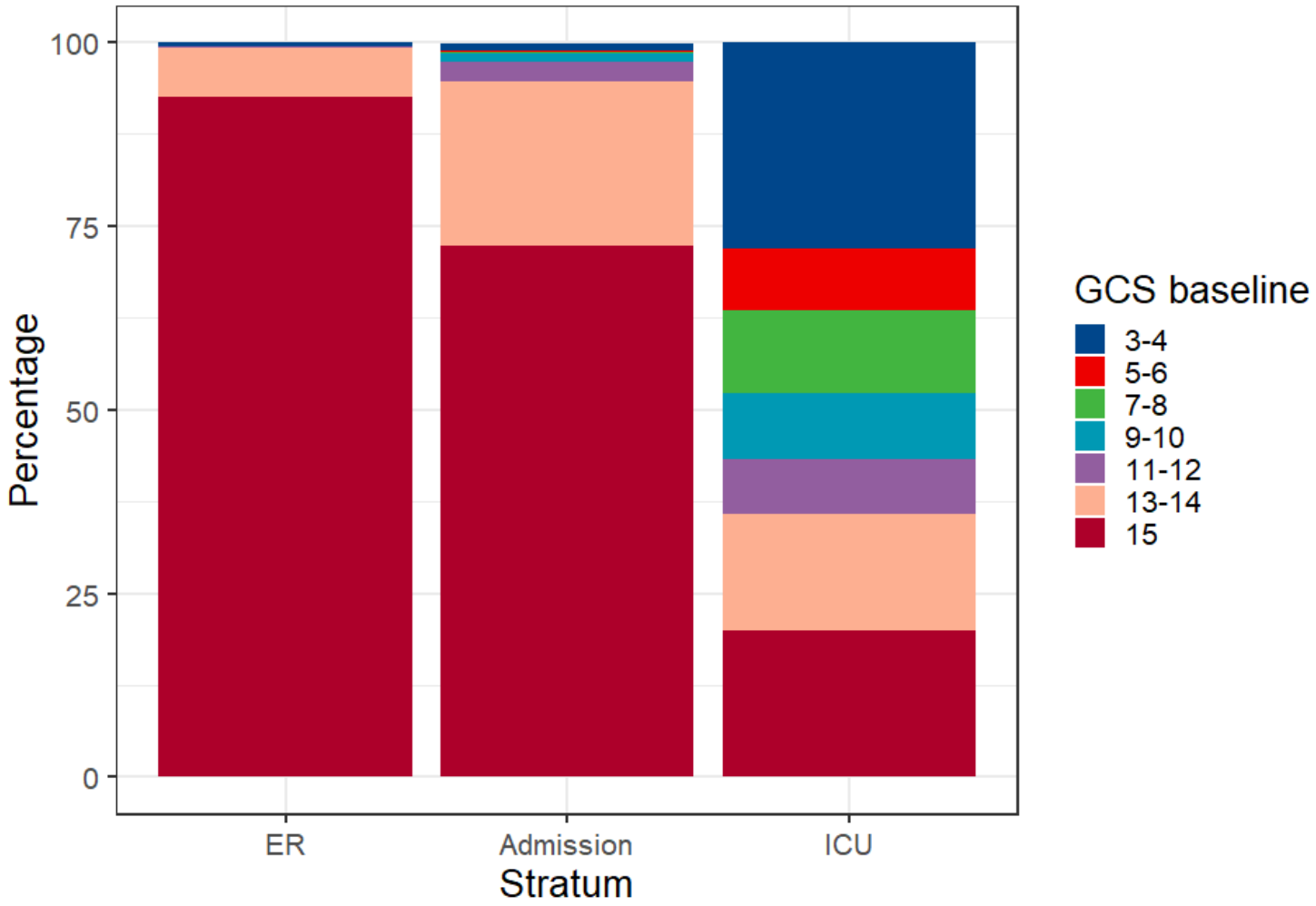
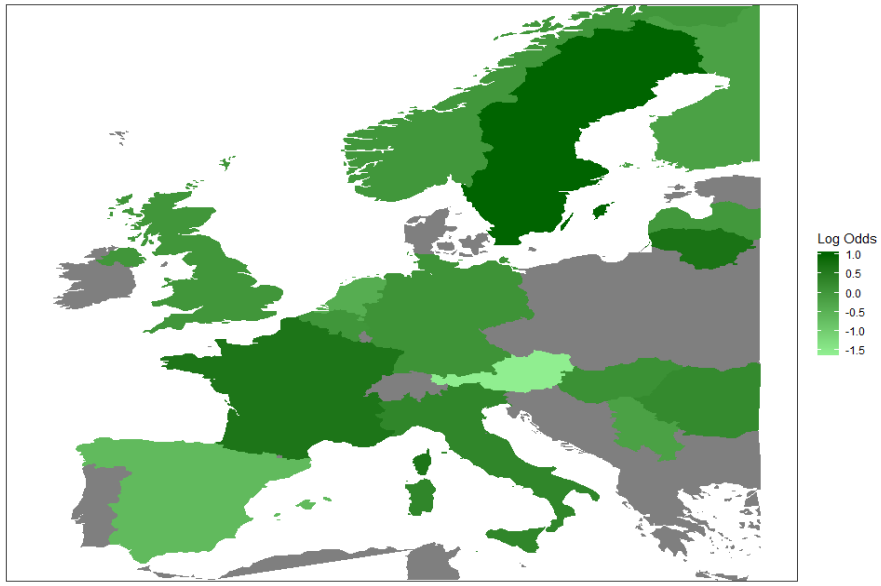
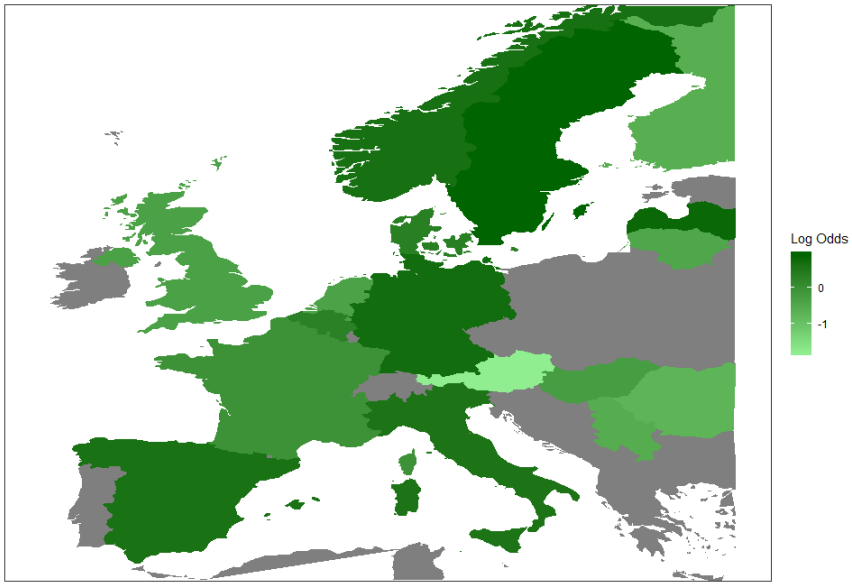


Figure 5: Between-country differences in processes of care for TBI in Europe. [1] performing intracranial surgery, [2] performing extracranial surgery, [3] the frequency of secondary referral, [4] frequency of placement of an ICP monitor in GCS<=8.

	
Log odds ratio of intracranial surgery, representing the log odds of intracranial surgery per contry compared to the overall average, adjusted for IMPACT CT model and stratum	Log odds ratio of extracrianal surgery, representing the log odds of extracranial surgery per contry compared to the overall average, adjusted for any major extracranial injury and stratum

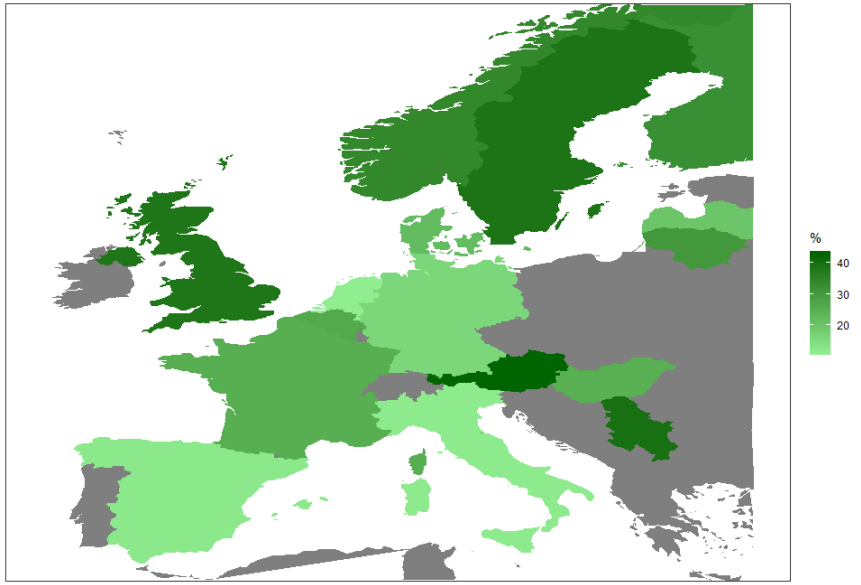
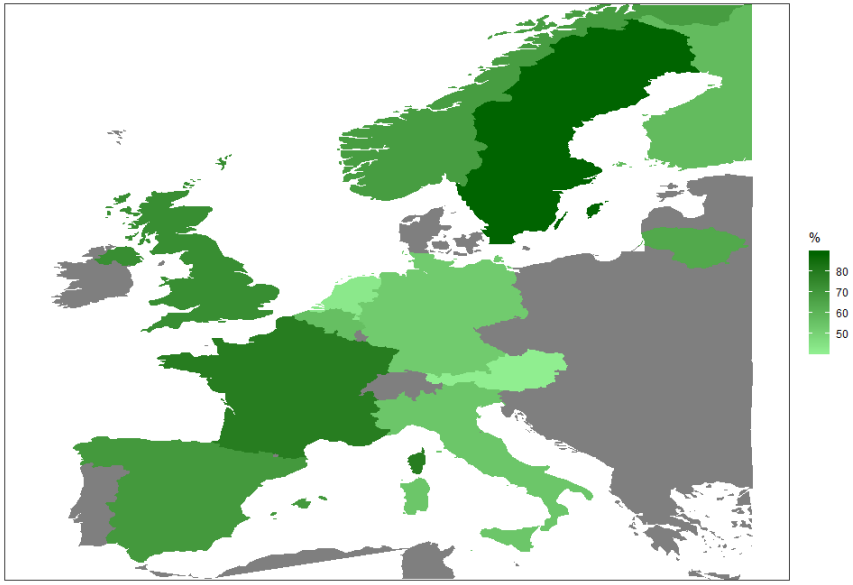
	
Percentage of patients in the ICU stratum (n = 2138) referred from another hospital per country	Percentage of patients with severe TBI (n= 958) with ICP monitor per country

Figure 6: 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, the majority of patients form the ER is discharged home while from the ICU most patients go to the ward. Abbreviations: ICU: Intensive Care Unit; ED: Emergency department. HCU: High Care Unit; OR: Operation Room; RU: Rehabilitation Unit; NH: Nursing Home.

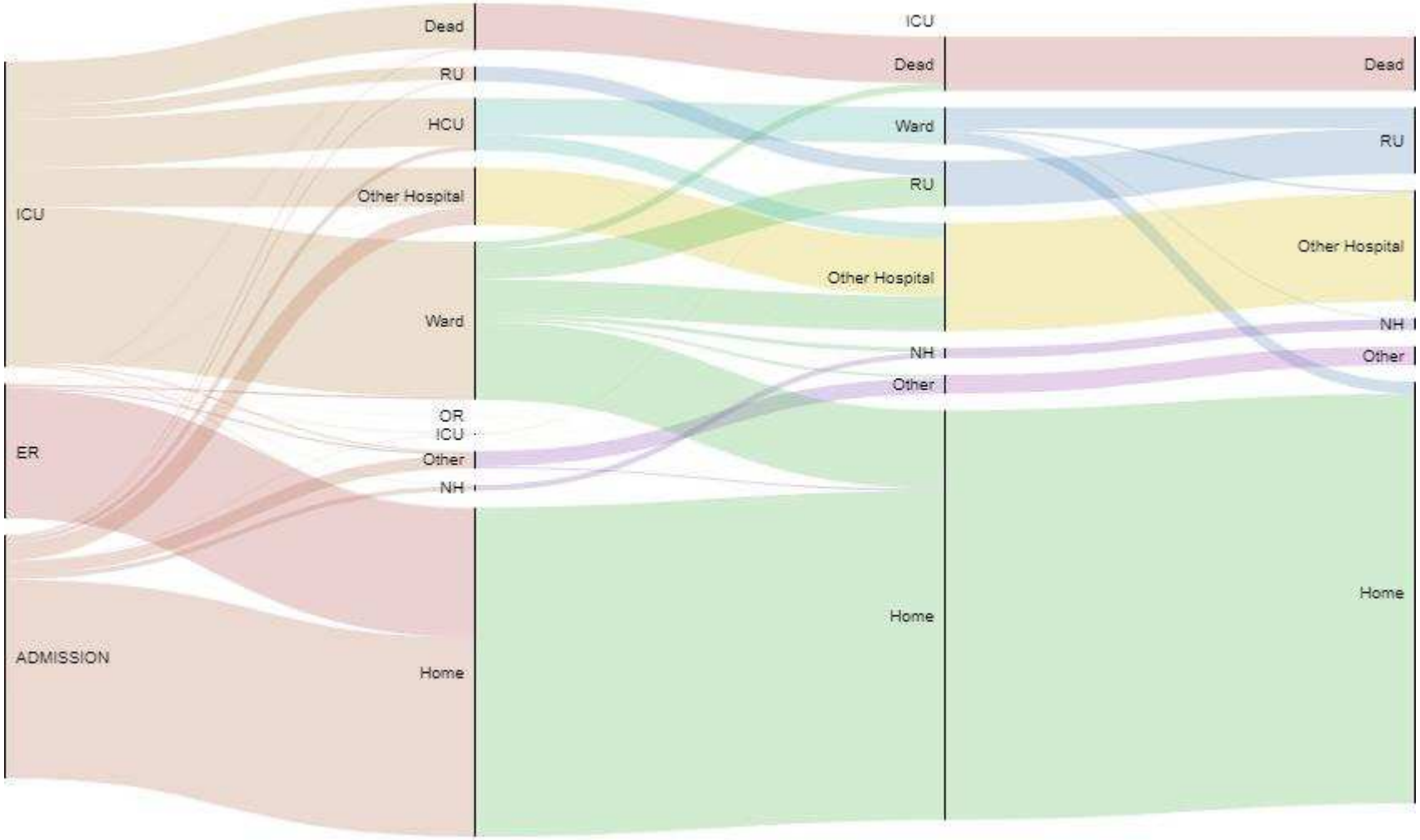
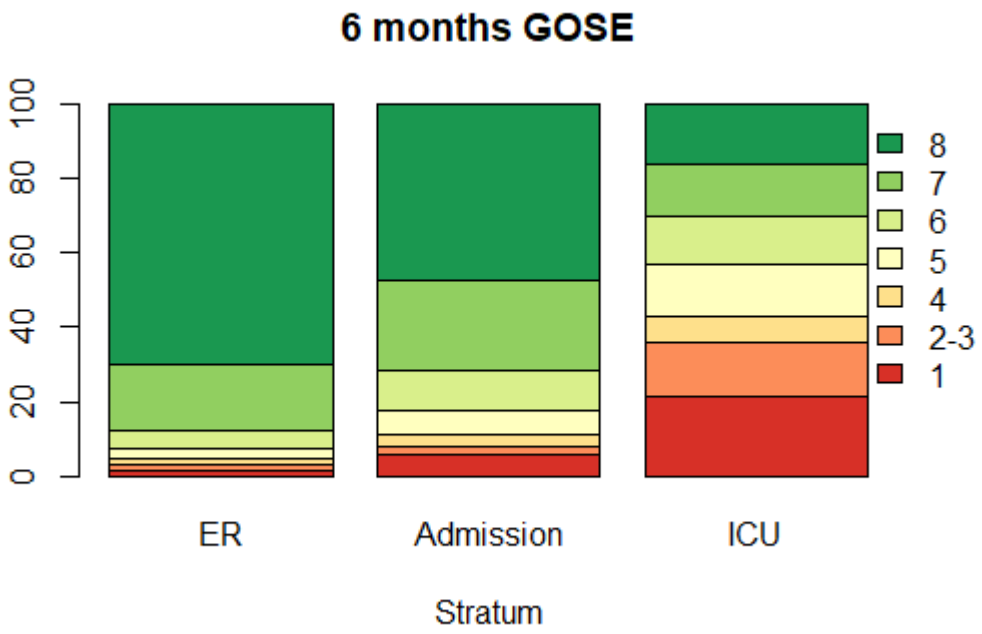


Figure 7: GOSE at 6 months by stratum in the Center-TBI Core study (ER *n*=694; Admission *n*=1264; ICU *n*=1846).
GOSE 1 = dead; GOSE 8 = Upper Good recovery; GOSE categories 2 (Vegetative) and 3 (Lower Severe Disability) are combined as differentiation is not possible for assessments performed by postal questionnaire.



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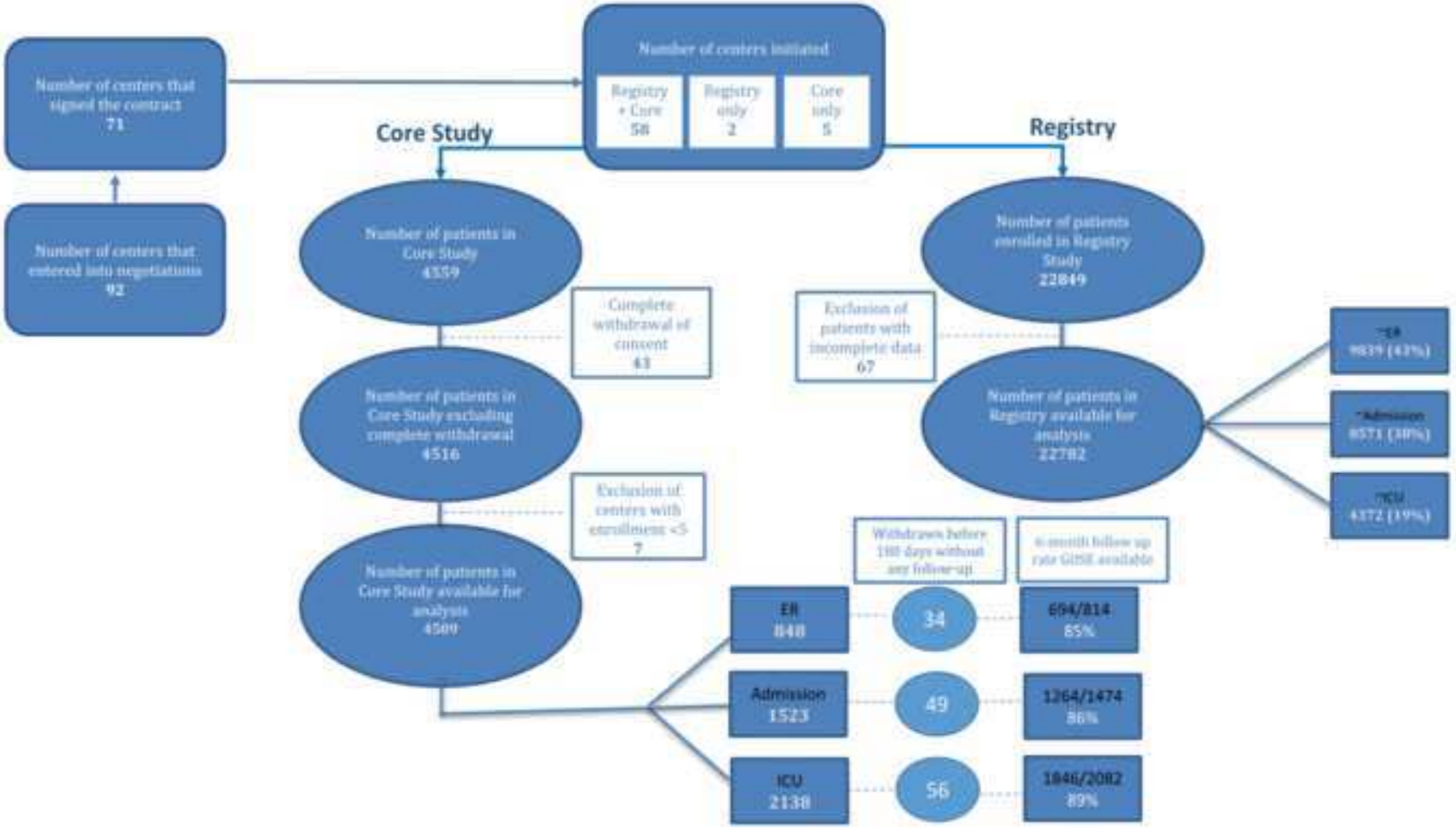

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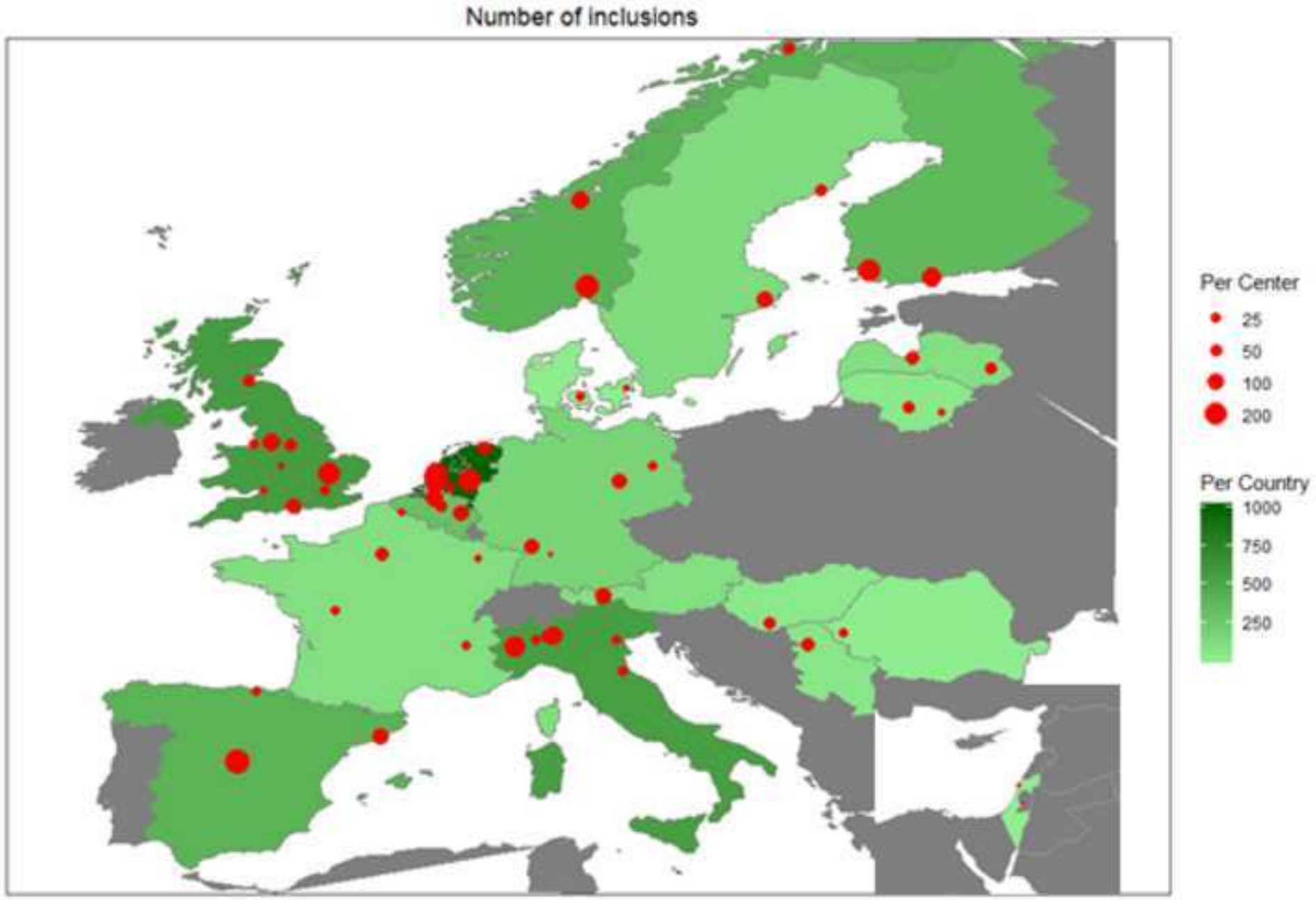

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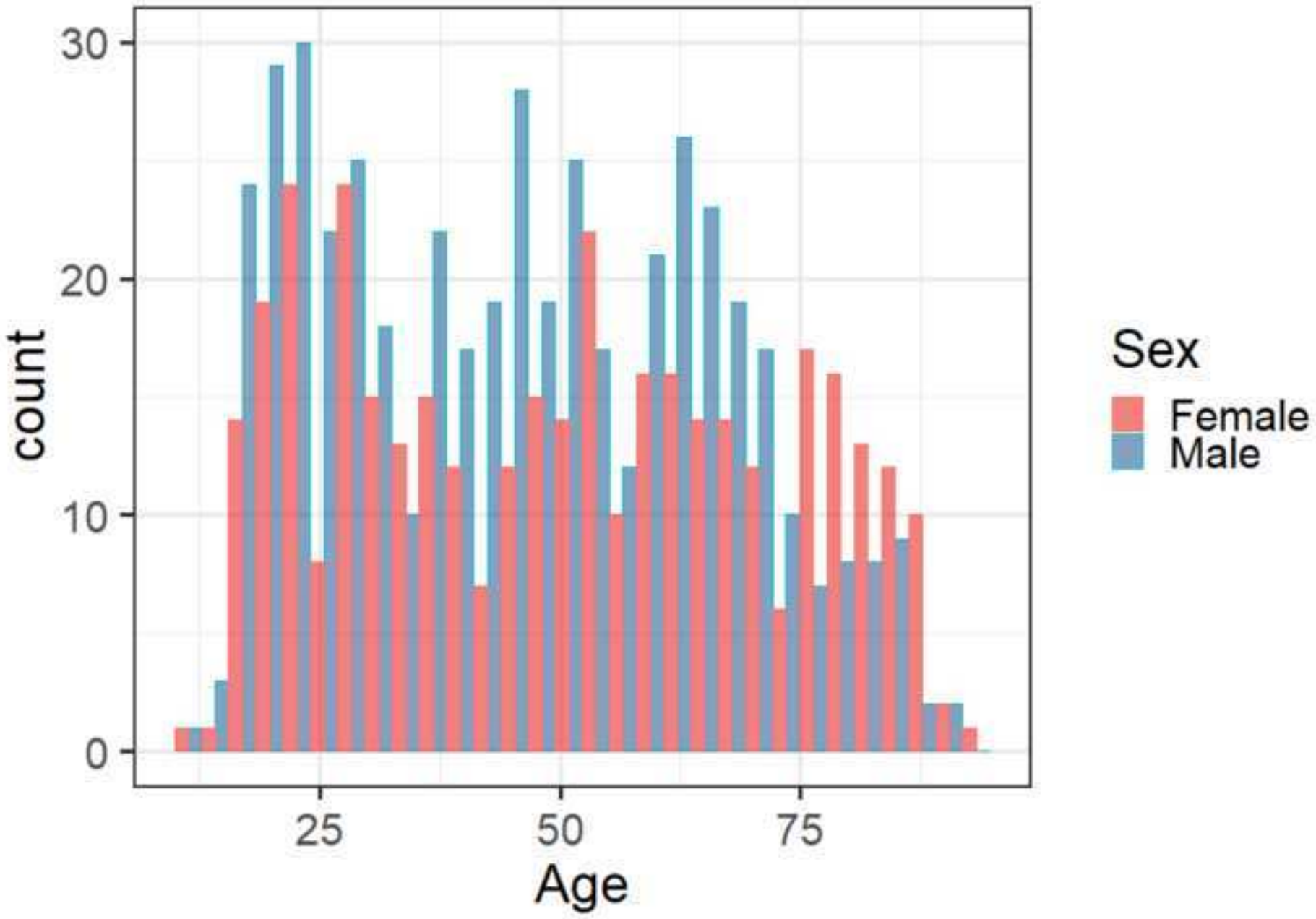

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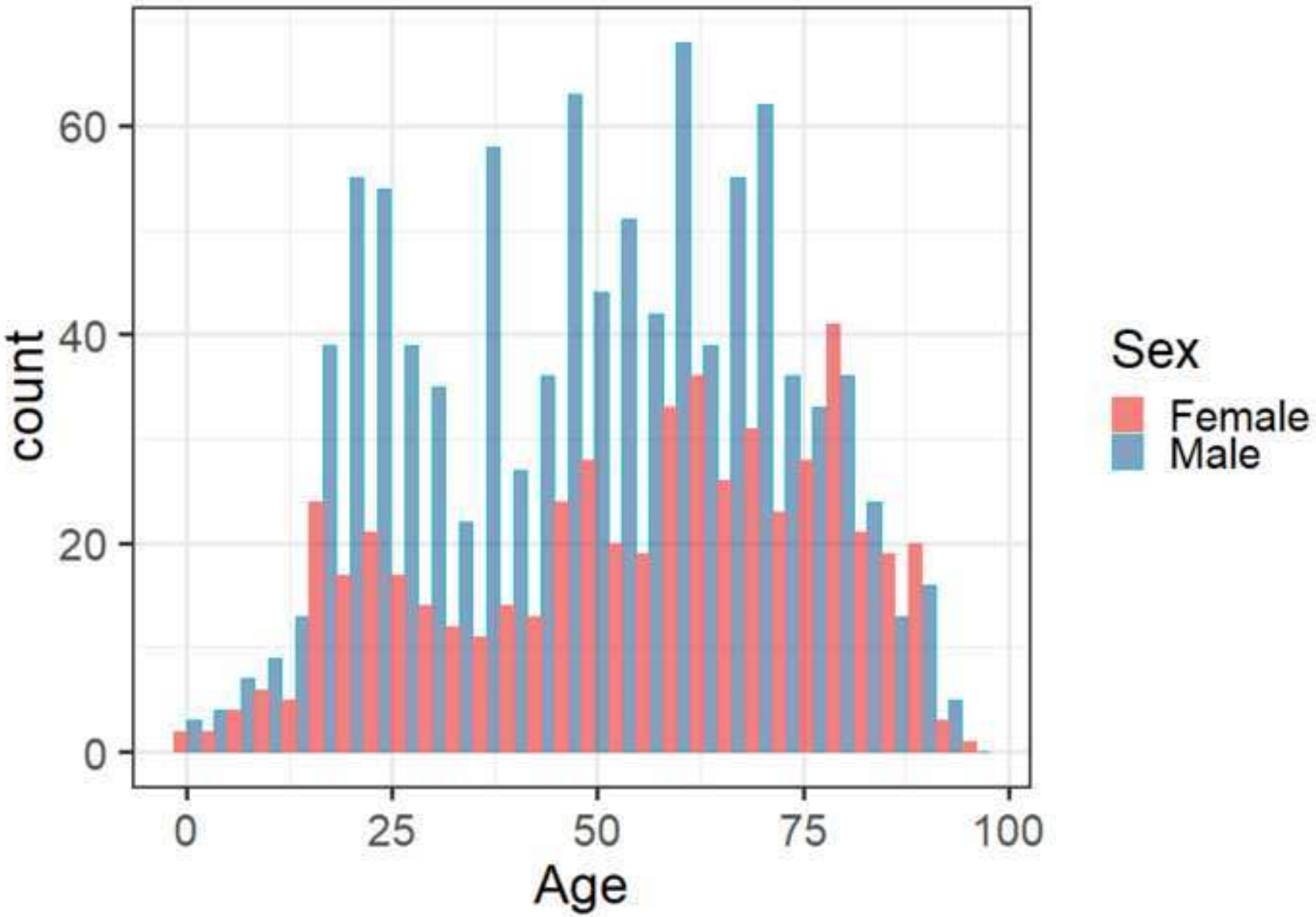

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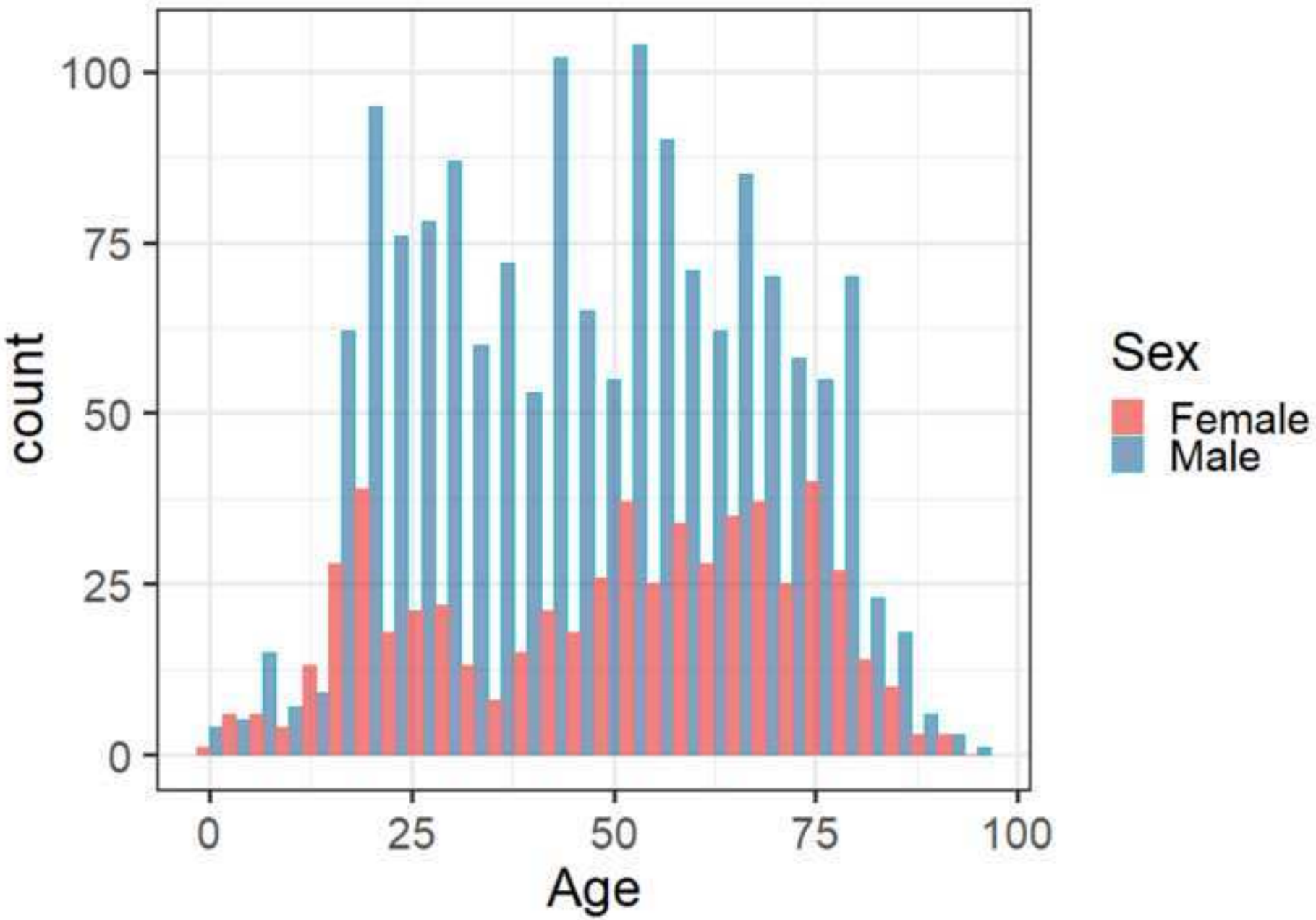

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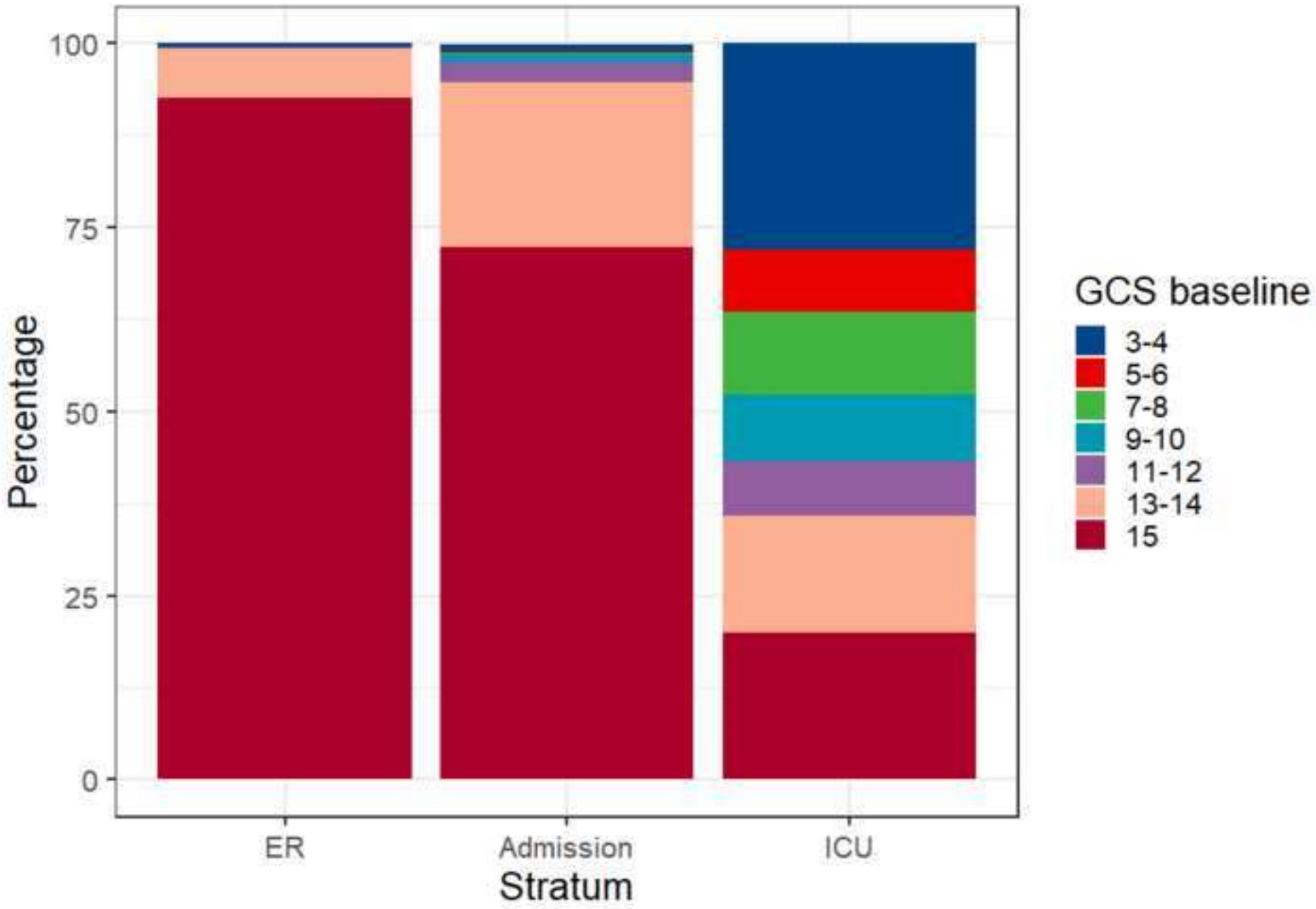

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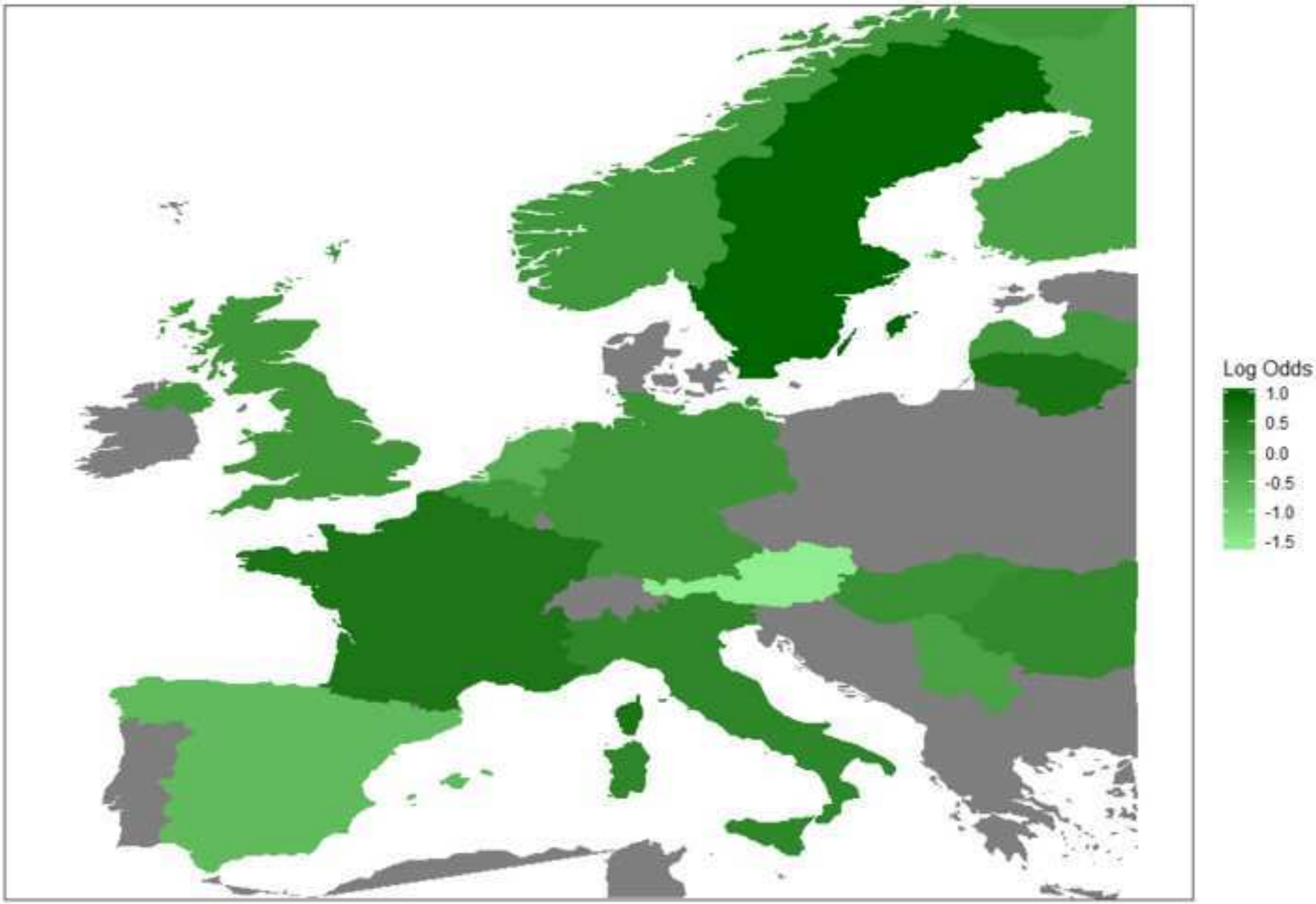

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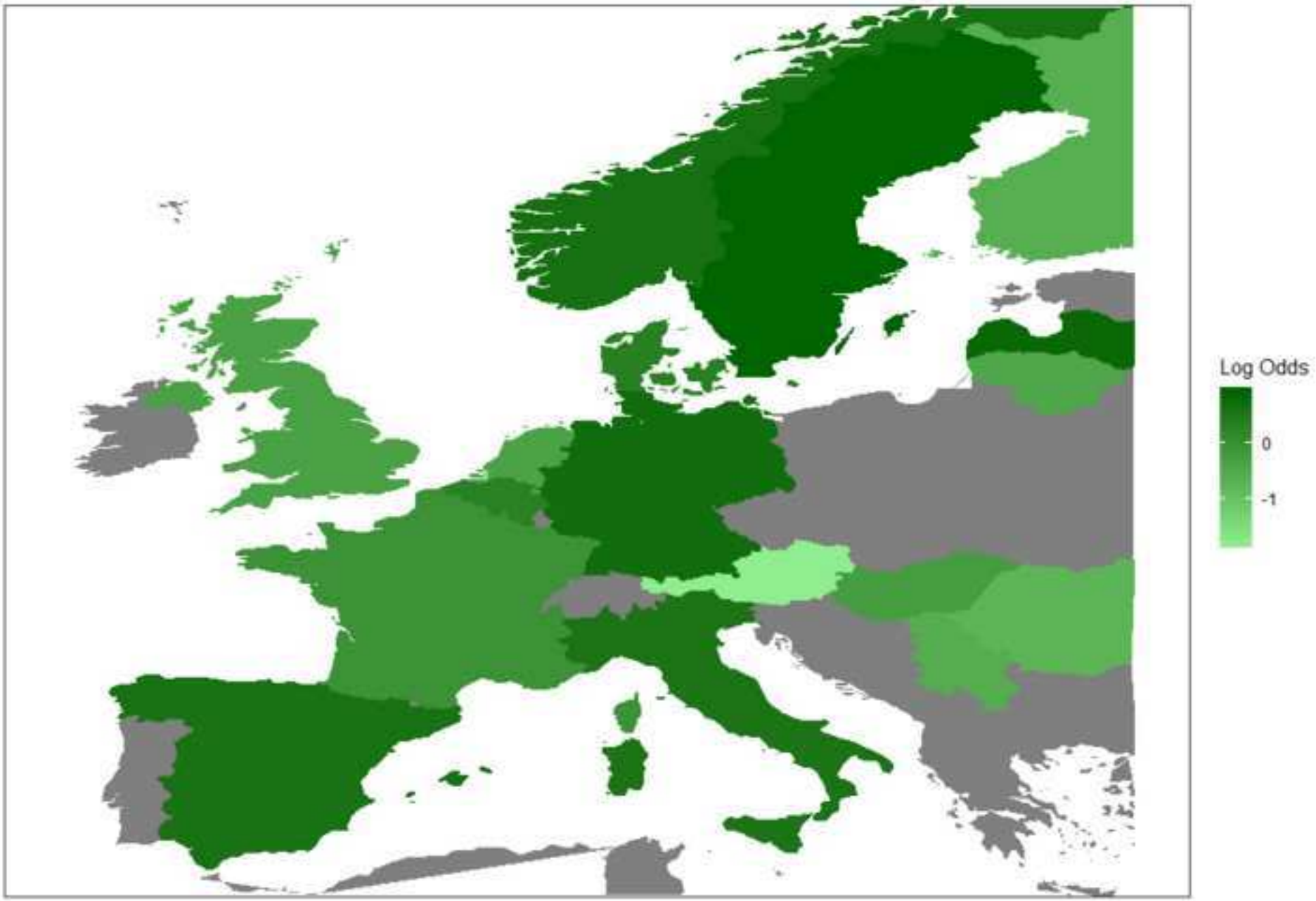

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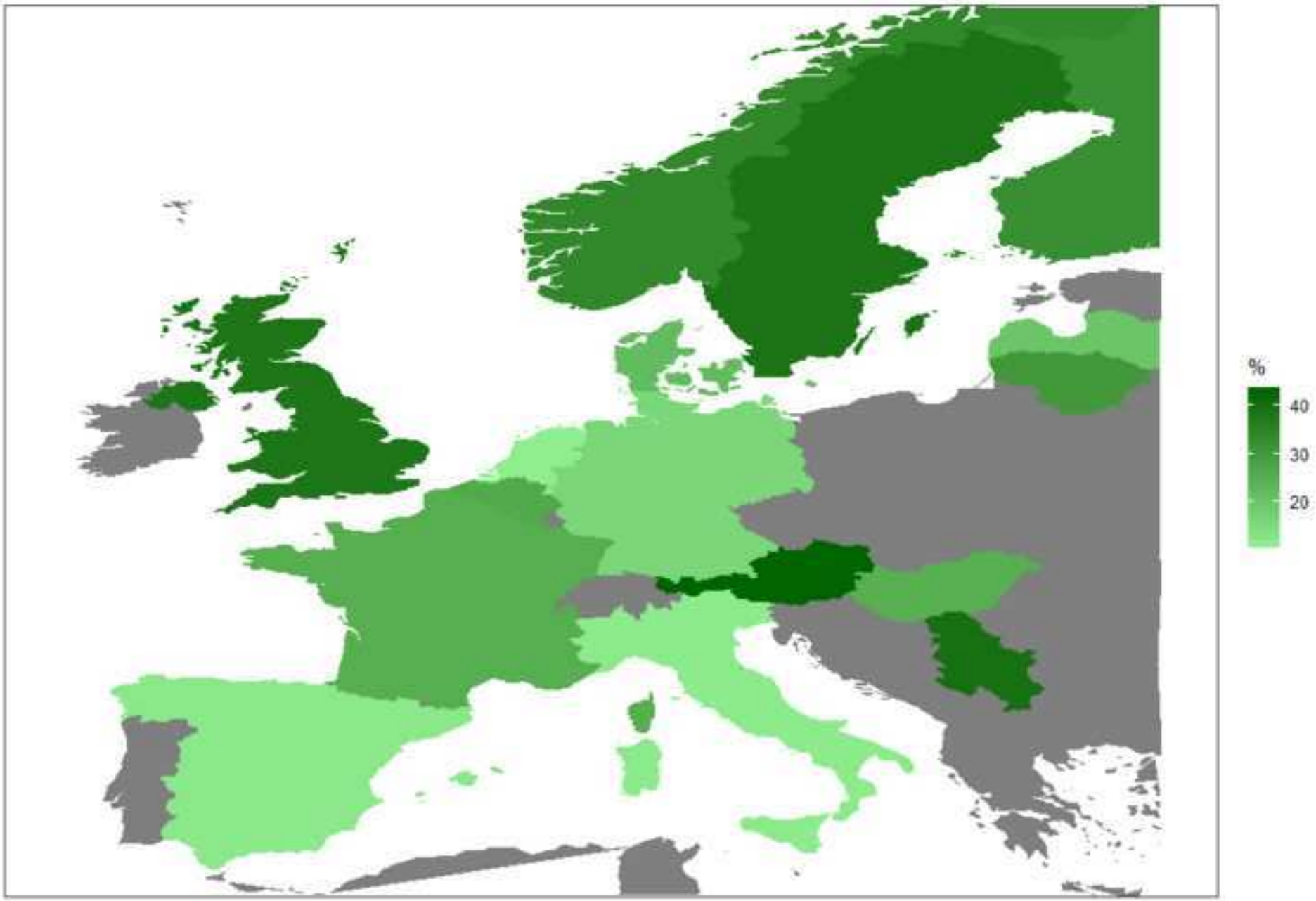

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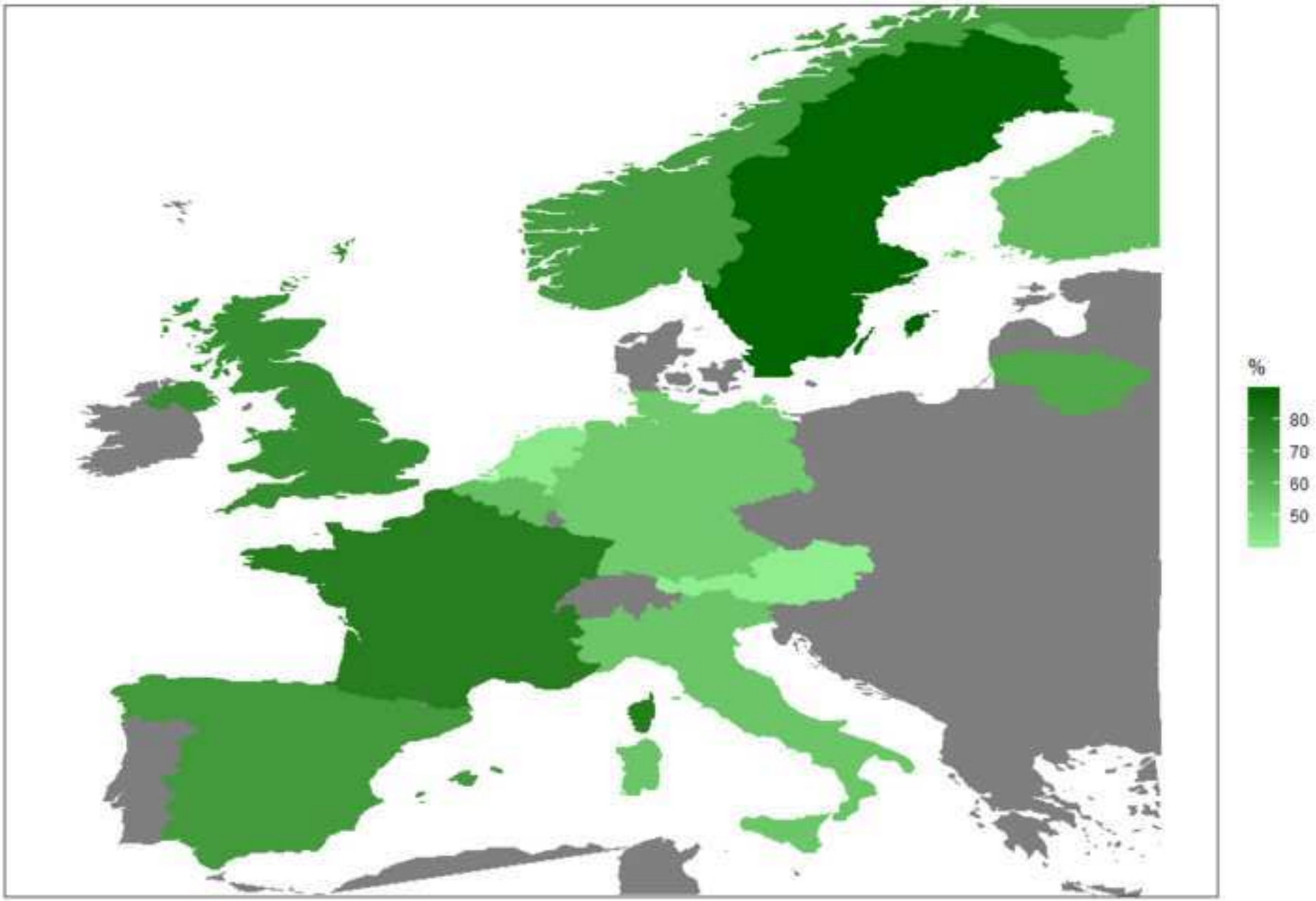

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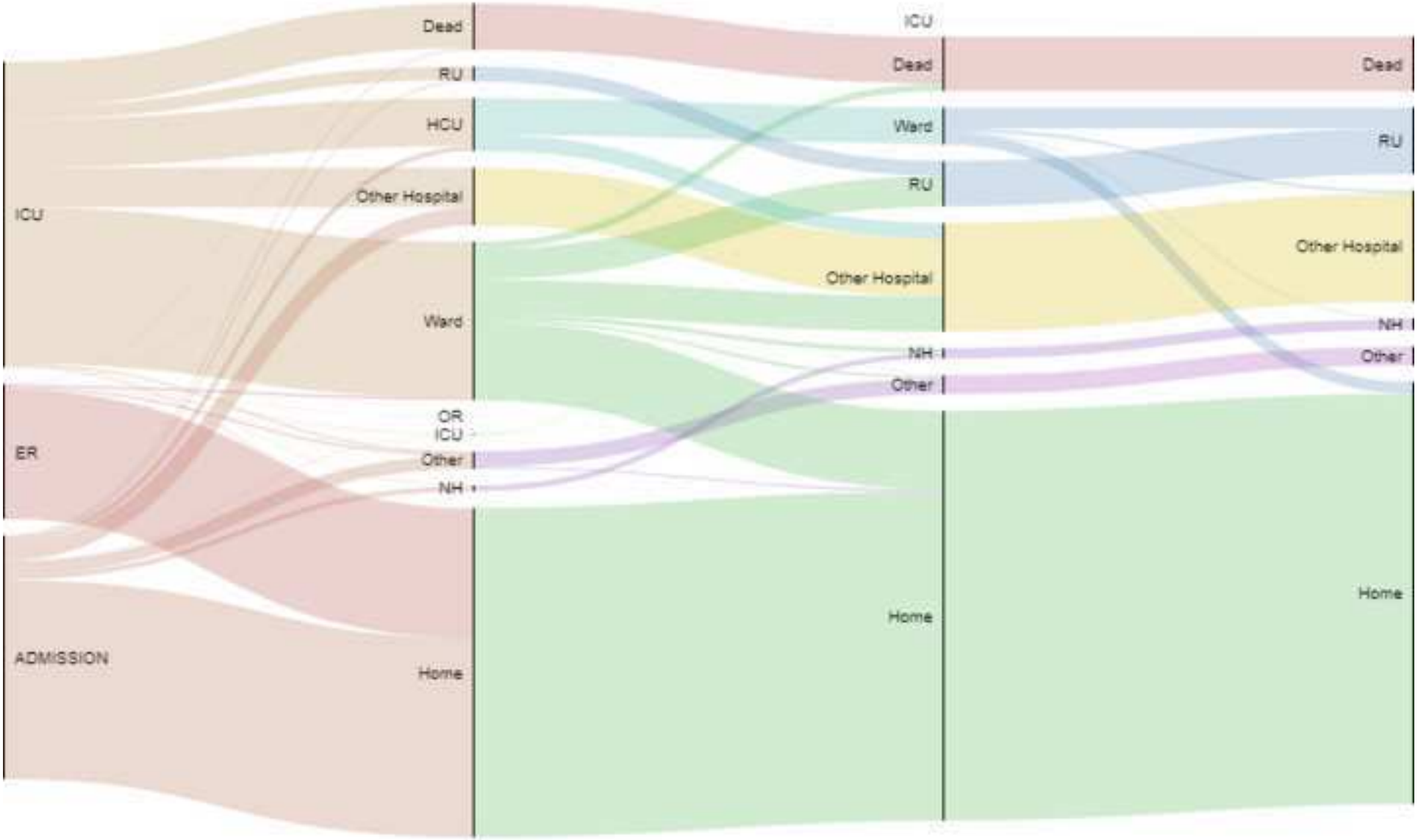

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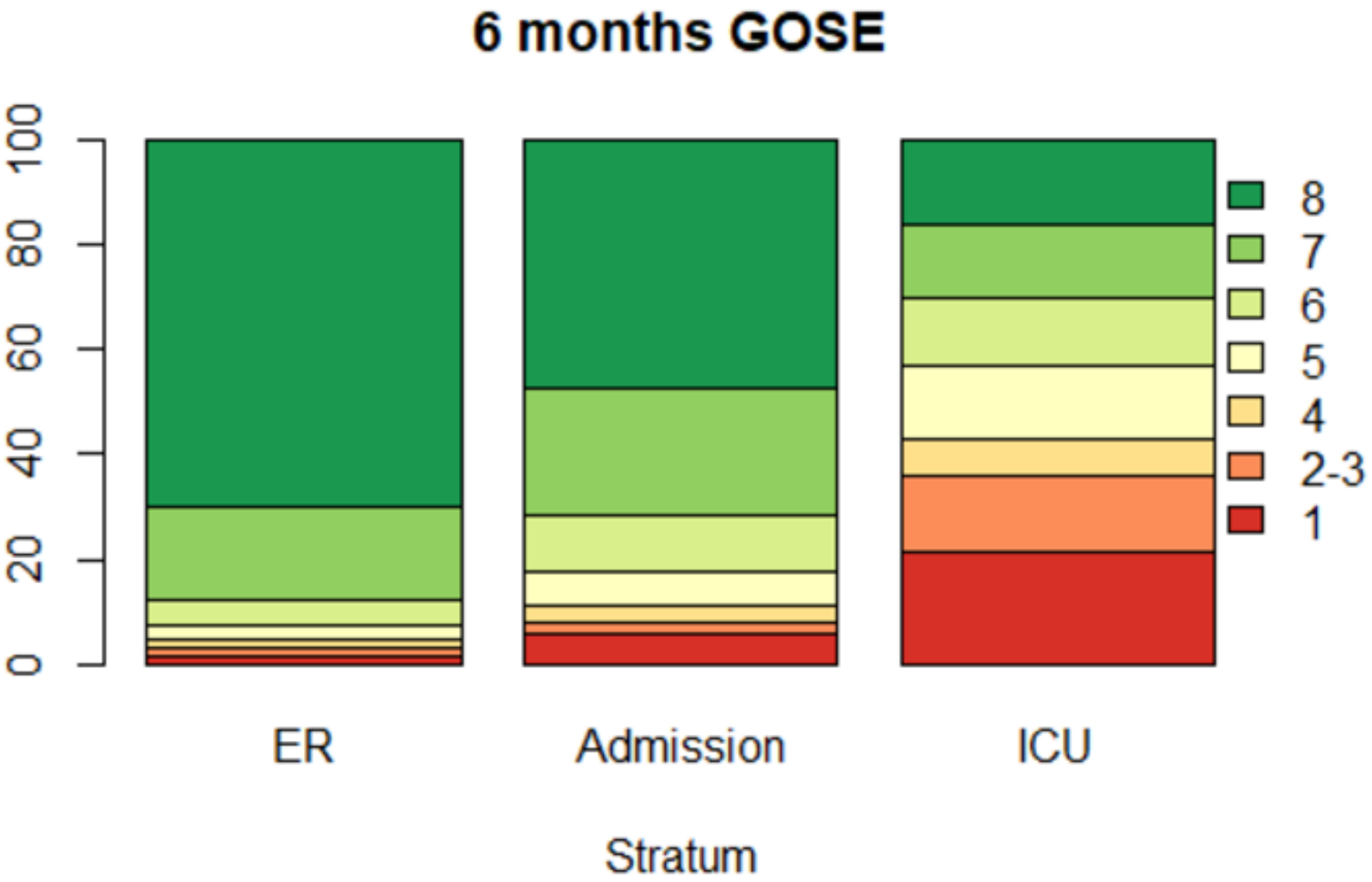


Suplemental material

Table S1: Socio-economic characteristics

Variable	N complete	N (%)	ER (N, %)	Admission (N, %)	ICU (N, %)	p-value*
		4509	848 (19%)	1523 (34%)	2138 (47%)	
Years of education (median, IQR)	3212	13 (10 – 16)	13 (11 – 16)	13 (11 – 16)	12 (10 – 15)	<0·001
Highest level of education	3566					<0·001
• None or primary school		641 (18%)	141 (18%)	224 (17%)	276 (19%)	
• Currently in or with diploma/degree oriented program		814 (23%)	152 (19%)	324 (25%)	338 (23%)	
• Secondary school		1261 (35%)	258 (33%)	422 (32%)	581 (39%)	
• College / University		850 (24%)	236 (30%)	334 (26%)	280 (19%)	
Marital status	4075					
• Married/living together		2070 (51%)	385 (48%)	717 (50%)	968 (52%)	0·15
Employment status before injury	3980					0·05
• Working		1946 (49%)	427 (52%)	638 (45%)	881 (50%)	
• Unable to work/sick leave		127 (3·2%)	23 (2·8%)	46 (3·3%)	58 (3·3%)	
• Retired		1112 (28%)	208 (26%)	438 (31%)	466 (27%)	
• Looking for work		235 (5·9%)	48 (5·9%)	88 (6·2%)	99 (5·7%)	
• Student / schoolgoing		486 (12%)	92 (11%)	174 (12%)	220 (13%)	
• Homemaker		74 (1·9%)	18 (2·2%)	30 (2·1%)	26 (1·5%)	

* p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively

Table S2: Pre-injury health status and medical history

	N complete	All (N, %)	ER (N, %)	Admission (N, %)	ICU (N, %)	p-value*
		4509	848 (19%)	1523 (34%)	2138 (47%)	
Pre-injury ASA-PS classification	4373					0·56
• A normal healthy patient		2501 (57%)	482 (57%)	836 (56%)	1183 (58%)	
• A patient with mild systemic disease		1410 (32%)	268 (32%)	507 (34%)	635 (31%)	
• A patient with severe systemic disease		462 (11%)	93 (11%)	159 (11%)	210 (10%)	
Medical history						0·21
• Any	4370	2089 (48%)	413 (49%)	737 (49%)	939 (46%)	
• Cardiovascular disease	4375	1304 (30%)	235 (28%)	492 (33%)	577 (29%)	
• Endocrine disease	4369	583 (13%)	130 (16%)	206 (14%)	247 (12%)	
Diabetic Mellitus		339 (7·8%)	70 (8·3%)	123 (8·1%)	145 (6·8%)	
• Oncologic	4368	285 (6·5%)	63 (7·5%)	110 (7·3%)	112 (5·6%)	
• Pulmonary	4369	443 (10%)	83 (9·9%)	180 (12%)	180 (8·9%)	
• Psychiatric	4352	601 (14%)	127 (15%)	182 (12%)	292 (15%)	
Previous TBI / concussions						<0·001
• Previous TBI	4158	402 (9·7%)	120 (15%)	149 (10%)	133 (7·0%)	
Anticoagulants	4345	298 (6·9%)	46 (5·5%)	133 (8·8%)	119 (6·0%)	0·001
Platelet aggregation inhibitors	4345	474 (11%)	85 (10%)	178 (12%)	211 (11%)	0·38

ASA-PS = The American Society of Anesthesiologists (ASA) physical status classification system, Any Medical History = Cardiovascular disease, Endocrine disease, Oncologic disease, Pulmonary disease, Psychiatric disease, TBI = Traumatic Brain Injury.

* p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively

Table S3: Cause of injury and intoxications

	N complete	All (N, %)	ER (N, %)	Admission (N, %)	ICU (N, %)	p-value *
		4509	848 (19%)	1523 (34%)	2138 (47%)	
Cause of injury	4388					<0·001
• Road traffic incident		1682 (38%)	266 (32%)	490 (33%)	926 (45%)	
• Incidental fall		2024 (46%)	424 (51%)	761 (51%)	839 (41%)	
• Violence / assault		245 (5·6%)	61 (7·3%)	100 (6·7%)	84 (4·1%)	
• Suicide attempt		48 (1·1%)	1 (0·1%)	3 (0·2%)	44 (2·1%)	
• Other		389 (8·9%)	84 (10%)	145 (9·7%)	160 (7·8%)	
Alcohol involved in the injury (yes or suspected)	4163	1054 (25%)	137 (17%)	384 (27%)	533 (28%)	<0·001
Recreational drugs involved in the injury (yes or suspected)	3938	130 (3·3%)	12 (1·5%)	28 (2·0%)	90 (5·2%)	<0·001
Sedatives or sleeping pills involved in the injury (yes or suspected)	3883	92 (2·4%)	10 (1·2%)	31 (2·2%)	51 (3·0%)	0·020

* p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively

Table S4: Baseline clinical characteristics

	N complete	All (N, %)	ER (N, %)	Admission (N, %)	ICU (N, %)	p-value *
		4509 (100%	848 (19%)	1523 (34%)	2138 (47%)	
GCS baseline (median (IQR))	4330	15 (10-15)	15 (15-15)	15 (14-15)	9 (4-14)	<0·001
Mild (13-15)		2955 (68%)	826 (99%)	1409 (93%)	720 (36%)	
Moderate (9-12)		389 (9·0%)	2 (0·2%)	59 (3·9%)	328 (16%)	
Severe (3-8)		986 (23%)	4 (0·5%)	21 (1·4%)	961 (48%)	
GCS motor score	4397					<0·001
M1-3		828 (18,9%)	4 (0·5%)	20 (1·3%)	804 (38·9%)	
M4		158 (3·6%)	3 (0·4%)	9 (0·6%)	146 (7·0%)	
M5		433 (9·8%)	9 (1·1%)	45 (3·0%)	379 (18·3%)	
M6		2978 (68%)	819 (98%)	1417 (95%)	742 (36%)	
Pupillary reactivity	4247					<0·001
One pupil unreactive		164 (3·9%)	3 (0·4%)	27 (1·9%)	134 (6·6%)	
Two pupils unreactive		281 (6·6%)	16 (2·0%)	19 (1·3%)	246 (12%)	
LOC (yes or suspected)	3987	2634 (66%)	391 (49%)	883 (64%)	1360 (75%)	<0·001
PTA (yes or suspected)	3092	1483 (48%)	284 (35%)	681 (50%)	518 (58%)	<0·001
Hypoxia (prehospital/ER phase)	4256	299 (7·0%)	3 (0·4%)	30 (2·1%)	266 (13%)	<0·001
Hypotension (prehospital/ER phase)	4296	297 (6·9%)	4 (0·5%)	26 (1·8%)	267 (13%)	<0·001
ISS (median (IQR))	4453	16 (9-29)	4 (2-8)	10 (9-17)	29 (25-41)	<0·001
Major extracranial injury (AIS >=3)						<0·001
Any	4509	1642 (36%)	46 (5·4%)	422 (28%)	1174 (55%)	
Face	4509	650 (14%)	19 (2·2%)	160 (11%)	471 (22%)	
Thorax/chest	4509	886 (20%)	8 (0·9%)	136 (8·9%)	742 (35%)	
Abdomen/pelvis	4509	422 (9·4%)	7 (8·3%)	56 (3·7%)	359 (17%)	
Extremities	4508	513 (11%)	17 (2·0%)	124 (8·1%)	372 (17%)	
External	4509	92 (2·0%)	8 (0·9%)	21 (1·4%)	63 (2·9%)	
Spine	4509	480 (11%)	10 (1·2%)	96 (6·3%)	374 (18%)	

GCS= Glasgow Coma, M = Motor, LOC = Loss of Consciousness, PTA = Post-Traumatic Amnesia, ISS = Injury Severity Score, AIS = Abbreviated Injury Scale (AIS).

* p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively

Table S5: Characteristics of patients enrolled in the Center-TBI Registry versus Center-TBI Core study.·

	ER		Admission		ICU	
	Core	Registry	Core	Registry	Core	Registry
	848 (19%)	9839 (43%)	1523 (34%)	8571 (38%)	2138 (47%)	4372 (19%)
Demographic characteristics						
Age (median, (IQR))	48 (29 – 64)	50 (29 - 72)	53 (32 – 69)	64 (40 - 81)	49 (29 – 65)	51 (31 - 68)
Male sex	473 (56%)	5523 (56%)	988 (65%)	5133 (60%)	1561 (73%)	3169 (73%)
Injury characteristics						
- Road traffic accident	266 (32%)	2191 (24%)	490 (33%)	2077 (25%)	926 (45%)	1636 (39%)
- Incidental fall	424 (51%)	4851 (52%)	761 (51%)	5237 (64%)	839 (41%)	2039 (49%)
- Other	146 (17%)	2244 (24%)	248 (17%)	910 (11%)	288 (14%)	496 (12%)
Baseline clinical characteristics						
GCS baseline (median, (IQR))	15 (15 – 15)	15 (15 – 15)	15 (14 – 15)	15 (14 – 15)	9 (4 – 14)	12 (5 – 15)
Mild (13-15)	826 (99%)	9276 (98%)	1409 (93%)	7735 (94%)	720 (36%)	1466 (49%)
Moderate (9 – 12)	2 (0·2%)	96 (10%)	59 (3·9%)	369 (4·5%)	328 (16%)	423 (14%)
Severe (3 – 8)	4 (0·5%)	55 (0·6%)	21 (1·4%)	113 (1·4%)	961 (48%)	1093 (37%)
GCS motor score (median, (IQR))	6 (6 – 6)	6 (6 - 6)	6 (6 – 6)	6 (6 - 6)	5 (1 – 6)	5 (1 - 6)
Pupillary reactivity						
- One pupil unreactive	3 (0·4%)	47 (0·5%)	27 (1·9%)	38 (0·5%)	134 (6·6%)	491 (12%)
- Two pupils unreactive	16 (2%)	81 (0·9%)	19 (1·3%)	126 (1·6%)	246 (12%)	303 (7·3%)
Major extracranial injury (AIS>=3)	46 (5·4%)	321 (3·3%)	422 (27%)	2410 (28%)	1174 (55%)	2312 (53%)
CT Characteristics						
Any intracranial abnormality	127 (15%)	498 (5·1%)	682 (49%)	3032 (36%)	1627 (89%)	3509 (81%)
Key emergency interventions						
Craniotomy for haemtoma/contusion	0 (0%)	6 (0%)	19 (1·2%)	124 (1·5%)	297 (14%)	700 (16%)
Arrived intubated at ED	2 (0·2%)	50 (0·5%)	15 (1·0%)	53 (0·6%)	929 (44%)	1776 (41%)
Status on discharge						
- In-hospital mortality	3 (0·4%)	75 (0·8%)	42 (2·8%)	209 (2·5%)	318 (15%)	773 (19%)

GCS = Glasgow Coma Scale, ICP = Intracranial pressure

Table S6: CT characteristics from central review

	N completed	All (N, %)	ER (N, %)	Admission (N, %)	ICU (N, %)	p-value *
Total number of patients		4509	848	1523	2138	
Marshall CT classification	4037	4037	835	1382	1820	<0·001
• Diffuse Injury I (no visible pathology)		1603 (39·7%)	708 (84·8%)	702 (51%)	193 (10.6%)	
• Diffuse Injury II		1558 (38·6%)	116 (13·9%)	569 (41%)	873 (48%)	
• Diffuse Injury III (swelling)		165 (4·1%)	1 (0·1%)	12 (0·9%)	152 (8·4%)	
• Diffuse Injury IV (shift)		32 (0·8%)	0 (0%)	4 (0·3%)	28 (1·5%)	
• V/VI (Evacuated/Non evacuated mass lesion)		679 (16·8%)	10 (1·2%)	94 (6·8%)	573 (31.5%)	
Any intracranial abnormality	4037	2434 (60%)	127 (15%)	680 (49%)	1627 (89%)	<0·001
Basal cistern absent / compressed	4037	648 (16%)	9 (1·1%)	60 (4·3%)	579 (32%)	<0·001
Midline shift	4037	465 (12%)	5 (1·0%)	61 (4·4%)	399 (22%)	<0·001
Traumatic subarachnoid haemorrhage (tSAH)	4037	1843 (46%)	81 (10%)	429 (31%)	1333 (73%)	<0·001
Epidural Hematoma	4037	480 (12%)	9 (1·1%)	110 (7·9%)	361 (20%)	<0·001
Acute subdural hematoma	4037	1241 (31%)	35 (4·2%)	310 (22%)	896 (49%)	<0·001
Diffuse Axonal Injury	4037	368 (9·1%)	18 (2·2%)	67 (4·8%)	283 (16%)	<0·001
Contusion	4037	1325 (33%)	41 (4·9%)	265 (19%)	1019 (56%)	<0·001

Any intracranial abnormality: Basal cistern absent / compressed, Midline shift, Traumatic subarachnoid haemorrhage, Epidural Hematoma, Acute subdural hematoma, Subacute/chronic subdural hematoma, Mixed density subdural hematoma, Contusion, Mass lesion, Intraventricular haemorrhage, and Traumatic axonal injury.

* p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively

Table S7. Agreement between central and local radiological evaluation of 3,922 admission CT scans.

	Agreement	Frequencies		Concordance		Discordance		
	Kappa (95% CI)	Central (N,%)	Site (N,%)	CR+/SR+	CR-/SR-	CR-/SR+	CR+/SR-	McNemar (p-value)
CT+	0.79 (0.77-0.81)	2358 (60%)	2408(61%)	2184	1340	224	174	0.014
Epidural hematoma	0.59 (0.55-0.63)	465 (12%)	419 (11%)	282	320	137	183	0.012
Acute subdural hematoma	0.67 (0.65-0.70)	1200 (31%)	1222 (31%)	936	2436	286	264	0.371
tSAH	0.67 (0.65-0.70)	1784 (45%)	1500 (38%)	1329	1967	171	455	0.001
Contusion	0.63 (0.60-0.65)	1278 (33%)	1366 (35%)	994	2272	372	284	0.001
TAI	0.35 (0.30-0.40)	359 (9%)	378 (10%)	152	3337	226	207	0.387
MLS	0.75 (0.71-0.78)	456 (12%)	576(15%)	402	3292	174	54	0.001
Cisternal compression	0.54 (0.50-0.58)	627 (16%)	351 (9%)	290	3234	61	337	0.001

Kappa values for a positive and negative CT scan (CT+, CT-, see methodology section) and 7 different CT characteristics. Frequencies in which CT characteristics were reported by the investigator sites and by the central review are shown, with associated McNemar tests for discordance of paired values. Frequencies of concordance and discordance are also shown. CR = Central Review, SR = Site Review. tSAH = Traumatic Subarachnoid Hemorrhage, TAI = Traumatic Axonal Injury, MLS = Midline Shift, CI = Confidence Interval.

Table S8: CT and MR agreement for 384 MR early (<3 weeks) scans (derived from central review)

	Agreement	Frequencies		Concordance		Discordance		
	Kappa (95% CI)	CT (N,%)	MR (N,%)	CT+/MR+	CT-/MR-	CT+/MR-	CT-/MR+	McNemar (p-value)
Any intracranial abnormality	0·52 (0·44-0·61)	182 (47%)	210 (55%)	142	150	32	60	0·005
No intracranial abnormality	0·52 (0·44-0·61)	202 (53%)	174 (45%)	150	142	60	32	0·005
Epidural hematoma	0·64 (0·49-0·79)	34 (9%)	23 (6%)	15	346	15	4	0·022
Acute subdural hematoma	0·47 (0·36-0·58)	75 (20%)	81 (21%)	45	273	30	36	0·538
tSAH	0·48 (0·39-0·58)	122 (32%)	90 (23%)	66	238	56	24	0·001
Contusion	0·65 (0·57-0·74)	84 (22%)	121 (32%)	76	255	8	45	0·001
TAI	0·15 (0·08-0·22)	21 (5%)	135 (35%)	18	246	3	117	0·001
MLS	0·28 (0·05-0·50)	19 (5%)	8 (2%)	4	361	15	4	0·022
Cisternal compression	0·29 (0·05-0·52)	17 (4%)	9 (2%)	4	362	13	5	0·099

Kappa values for Any intracranial abnormality and 7 different imaging characteristics. Frequencies in which the imaging characteristics were reported on CT and MR are shown, with associated McNemar tests for discordance of paired values. Frequencies of concordance and discordance are also shown. CT = Computed Tomography, MR = Magnetic Resonance. tSAH = Traumatic Subarachnoid Hemorrhage, TAI = Traumatic Axonal Injury, MLS = Midline Shift, CI = Confidence Interval.

Table S9: Diagnostic and Surgical interventions

	N completed	N (%)	ER (N, %)	Admission (N, %)	ICU (N, %)	p-value *
Total number of patients		4509	848 (19%)	1523 (34%)	2138 (47%)	
ICP monitor placed	2340	924 (43%)	0 (0·0%)	3 (7%)	921 (44%)	<0·001
Intracranial surgery	3686	885 (24%)	1 (2·4%)	64 (4·2%)	820 (39%)	<0·001
Total number of intracranial surgeries		1289	1	65	1224	
• Decompressive craniectomy		204 (16%)	0 (0·0%)	2 (3·1%)	202 (17%)	
• Depressed skull fracture		54 (4·2%)	0 (0·0%)	9 (14%)	45 (3·7%)	
• Acute subdural hematoma		323 (25%)	0 (0·0%)	14 (22%)	309 (25%)	
• Epidural hematoma		134 (10%)	0 (0·0%)	19 (29%)	115 (9·4%)	
• Intracerebral hematoma		32 (2·5%)	0 (0·0%)	1 (1·5%)	31 (2·5%)	
• Ventriculostomy for CSF drainage		162 (13%)	0 (0·0%)	1 (1·5%)	161 (13%)	
• Other		380 (30%)	1 (100%)	19 (29%)	360 (29%)	
Extracranial surgery	3685	735 (20%)	1 (2·4%)	128 (8·4%)	606 (29%)	<0·001
Total number of extracranial surgeries		1305	2	158	1145	
• Maxillofacial		177 (14%)	1 (50%)	36 (23%)	140 (12%)	
• Extremity fracture		457 (35%)	1 (50%)	56 (35%)	400 (35%)	
• Laparotomy		65 (5·0%)	0 (0·0%)	4 (2·5%)	61 (5·3%)	
• Pelvic fracture		64 (4·9%)	0 (0·0%)	5 (3·2%)	59 (5·2%)	
• Spinal stabilization		117 (9·0%)	0 (0·0%)	13 (8·2%)	104 (9·1%)	
• Thoracotomy		13 (1·0%)	0 (0·0%)	2 (1·3%)	11 (1·0%)	
• Other		412 (32%)	0 (0·0%)	42 (27%)	370 (32%)	

CSF = Cerebrospinal Fluid.

Percentage figures for individual types of surgical procedures are in relation to the total number of extracranial and intracranial surgeries performed (as appropriate in each context)

* p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively

Table S10: Glasgow Outcome Scale – Extended (GOSE) assessed during follow-up: known (*n*=3804) versus unknown (*n*=705)

Variable	GOSE available (N, %) 3804 (84%)	GOSE unknown (N, %) 705 (16%)	p-value *
Demographic characteristics			
Age (median (IQR))	51 (30-67)	46 (29-64)	0·023
• >=65 years	1078 (28%)	176 (25%)	0·056
Male sex	2530 (67%)	492 (69%)	0·174
Caucasian	3502 (97%)	626 (95%)	0·013
Socio-economic characteristics			
Years of education (median (IQR))	13 (10-16)	12 (10-15)	<0·001
Highest level of education			
• College / University	757 (25%)	93 (18%)	0·001
Married/living together	1790 (51%)	280 (48%)	0·0·09
Employment status before injury			
• Working	1661 (49%)	285 (49%)	0·002
Pre-injury health status and medical history			
Pre-injury ASA-PS classification			0·605
• A patient with mild systemic disease	1203 (22%)	207 (31%)	
• A patient with severe systemic disease	394 (11%)	68 (10%)	
Previous TBI	345 (10%)	57 (8·8%)	0·448
Anticoagulants	250 (6·8%)	48 (7·3%)	0·726
Platelet aggregation inhibitors	417 (11%)	57 (8·6%)	0·046
Cause of injury and use of medication			
Cause of injury			<0·001
• Road traffic incident	1454 (39%)	228 (33%)	
• Incidental fall	1715 (46%)	309 (45%)	
Alcohol involved in the injury (yes or suspected)	848 (24%)	206 (32%)	<0·001
Baseline clinical characteristics			
GCS baseline (median (IQR))	15 (9-15)	15 (12-15)	<0·001
GCS motor score (median (IQR))	6 (5-6)	6 (6-6)	<0·001

Pupillary reactivity			0·003
• One pupil unreactive	139 (3·9%)	25 (3·8%)	
• Two pupils unreactive	257 (7·2%)	24 (3·6%)	
Hypoxia (prehospital/ER phase)	270 (7·5%)	29 (4·3%)	0·003
Hypotension (prehospital/ER phase)	273 (7·5%)	24 (3·6%)	<0·001
Major extracranial injury (AIS >=3)			
Spine	427 (11%)	53 (7·5%)	0·003

ASA-PS = The American Society of Anesthesiologists (ASA) physical status classification system, TBI = Traumatic Brain Injury, GCS = Glasgow Coma Scale, AIS = Abbreviated Injury Scale (AIS).

* p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively

Figure S1: Enrolment in strata by centre. The width of the bars indicates the total number of patients per centre.

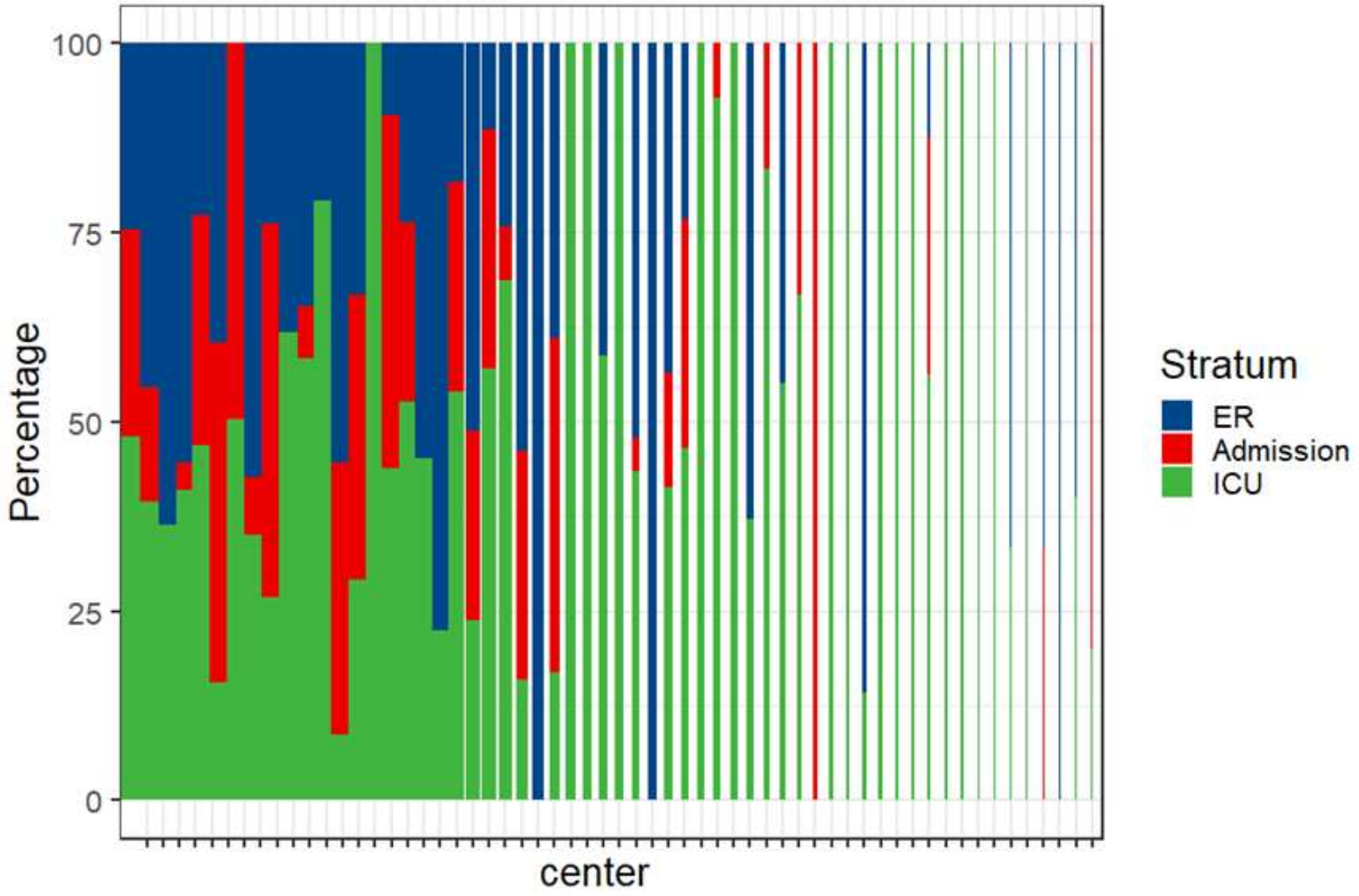


Figure S2: Cause of Injury by Age Group, CENTER-TBI Core

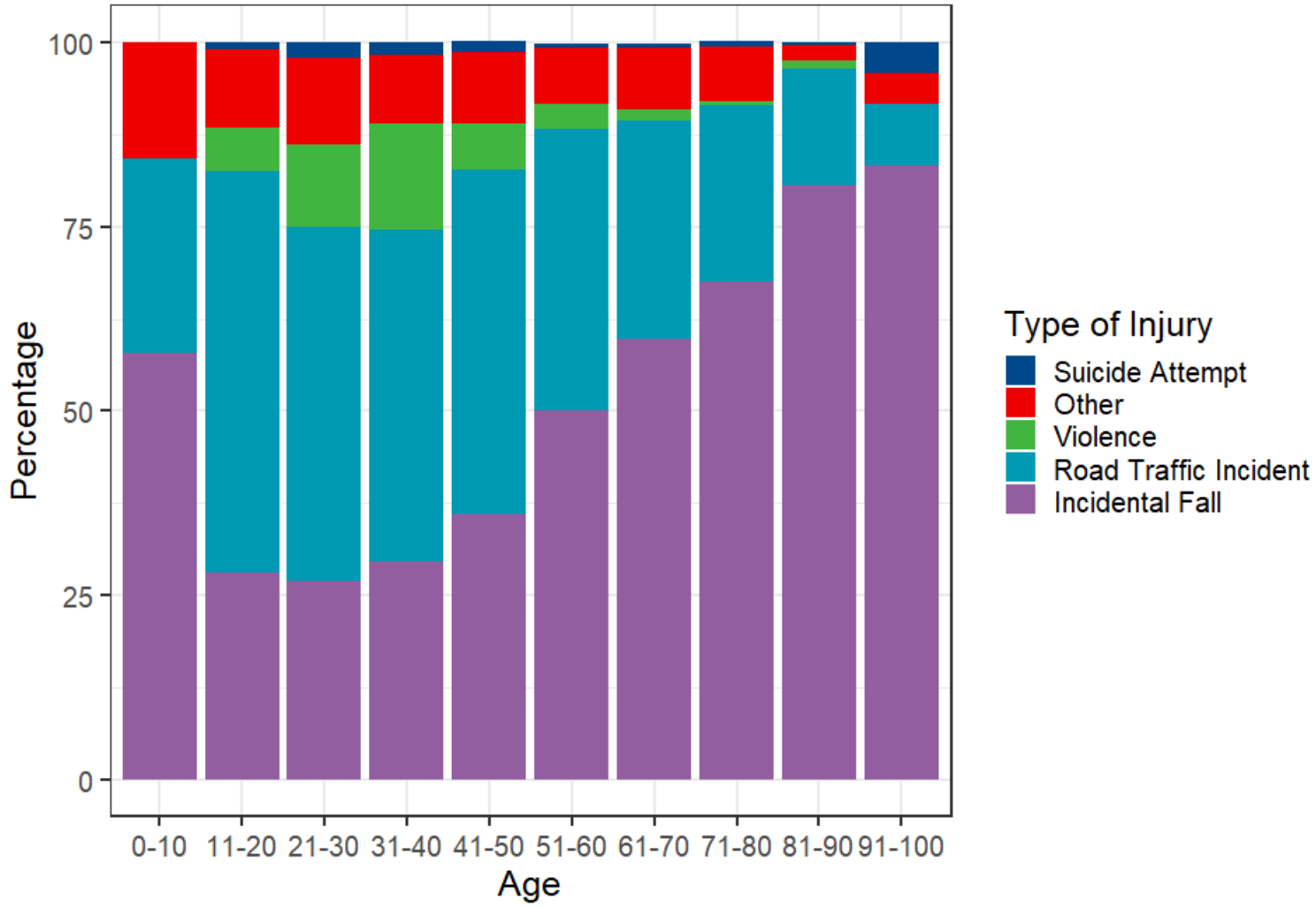
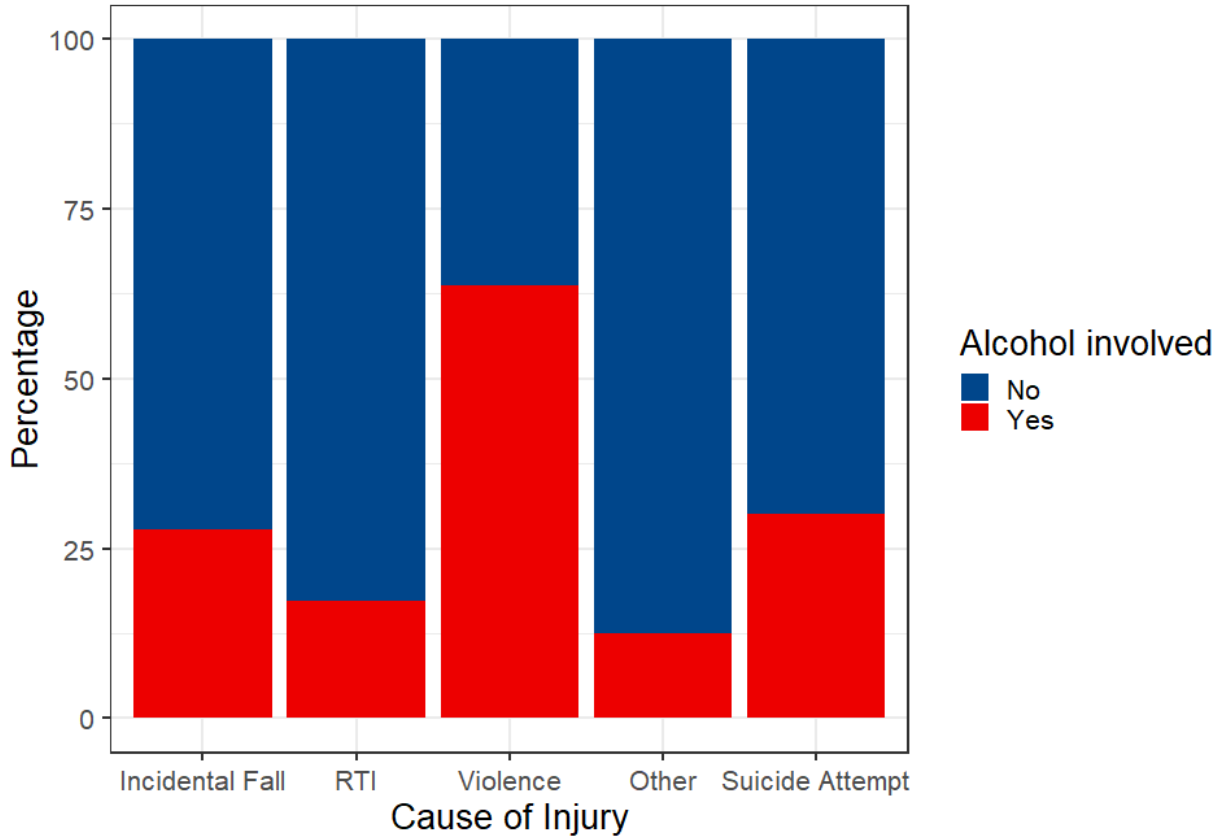
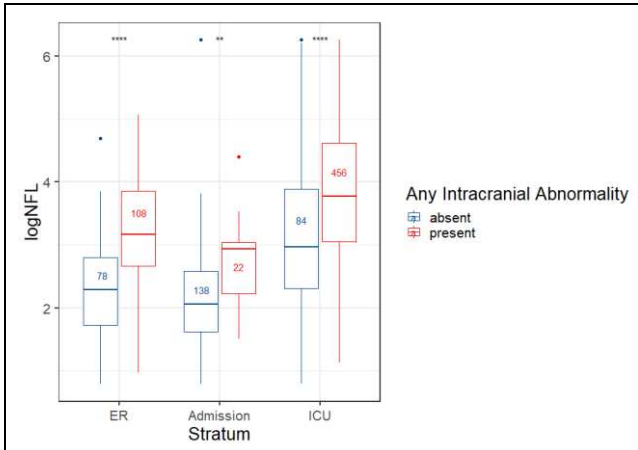
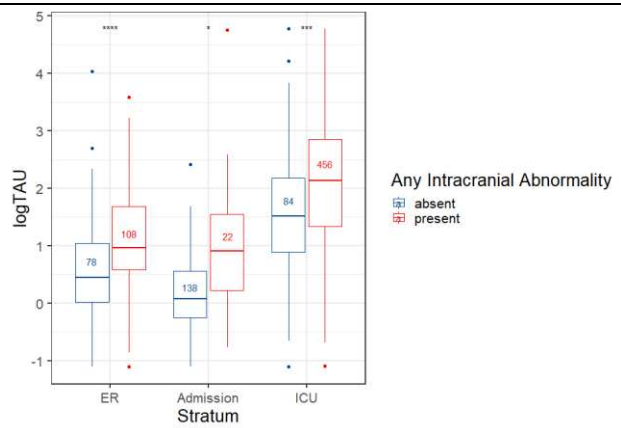
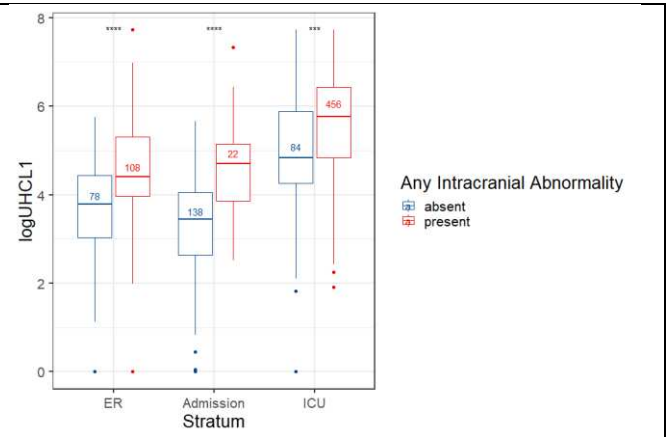
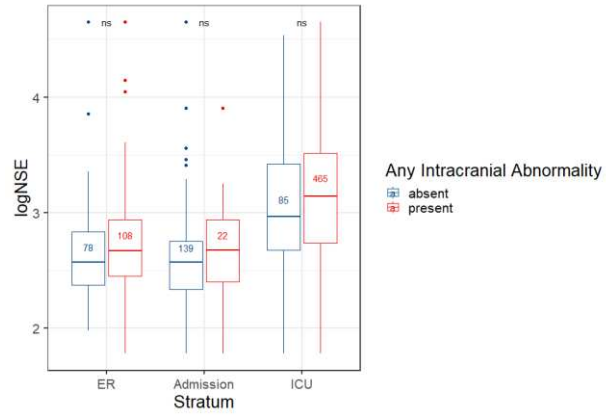
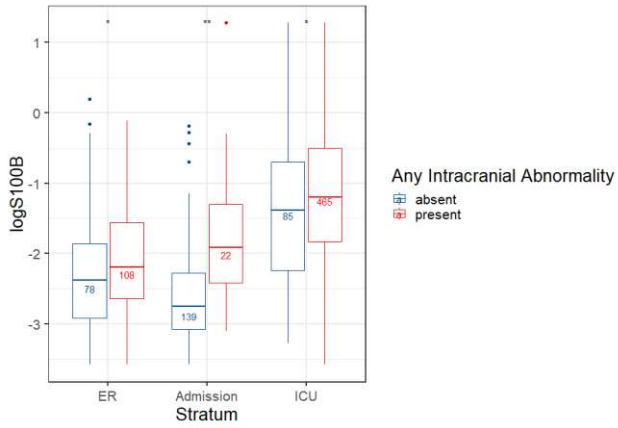
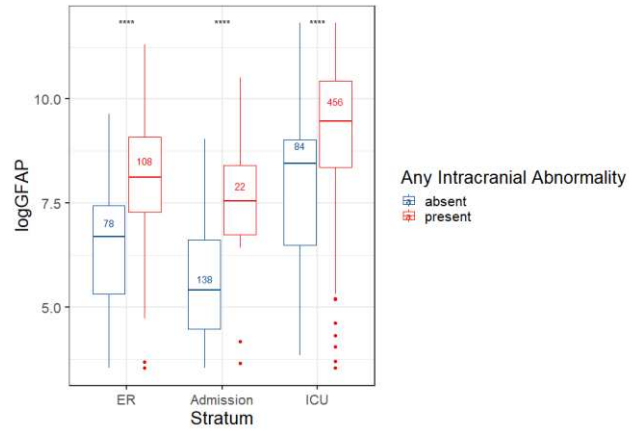


Figure S3 Alcohol use and Cause of Injury, CENTER-TBI Core



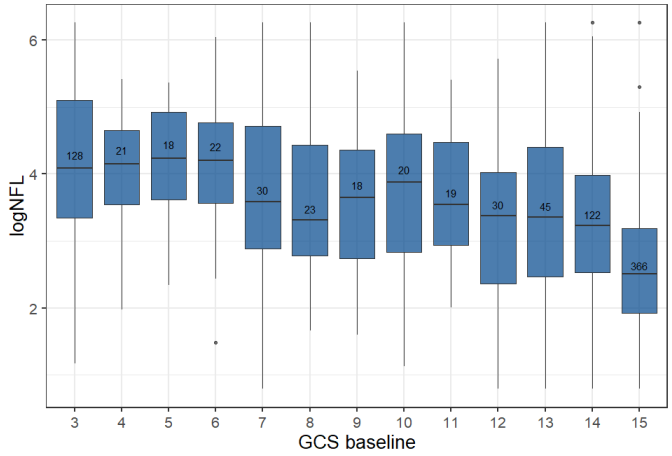
*RTI = Road Traffic Incident. Alcohol Involved in Incidental Fall: 533/1918 (28%), RTI: 262/1528 (17%), Violence: 144/226 (64%), Other: 45/359 (13%), Suicide Attempt: 12/40 (30%).

Figure S4: Biomarkers versus CT Abnormalities by stratum (complete cases analysis, n=898)

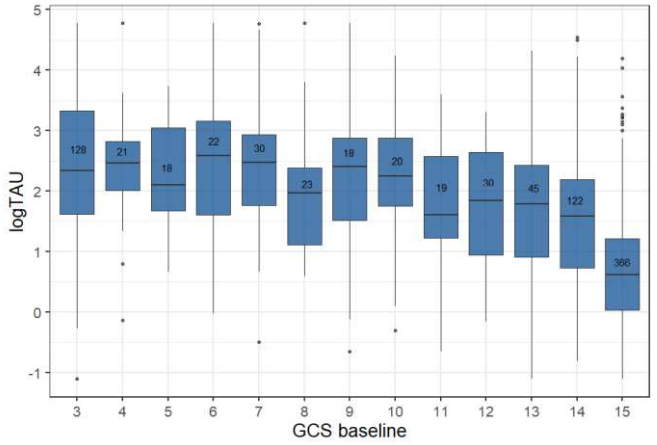
		
NFL = Neurofilament Light	t-TAU = total TAU	UCHL1 = Ubiquitin Carboxy-Terminal Hydrolase L1
		
NSE = Neuron-Specific Enolase	S100B = S100 calcium-binding protein B	GFAP = Glial Fibrillary Acidic Protein

[#] NSE and S-100B were measured on the e602 module of a Cobas 8000 analyzer (Roche Diagnostics International Ltd· Rotkreuz, Switzerland) in Pecs, Hungary and NF-L, total Tau, GFAP, and UCH-L1 on the Quanterix SIMOA Neurology 4-plex kit (Quanterix, Lexington, MA, USA), at the University of Florida, USA. Differences between biomarker values in patients with any intracranial abnormality versus patients without any intracranial abnormality were tested per stratum with a t-test. The stars above the bars indicate significance: ns: p>0·05, *: p<=0·05, **: p<=0·01, ***: p<=0·001, ****: p<=0·0001·.

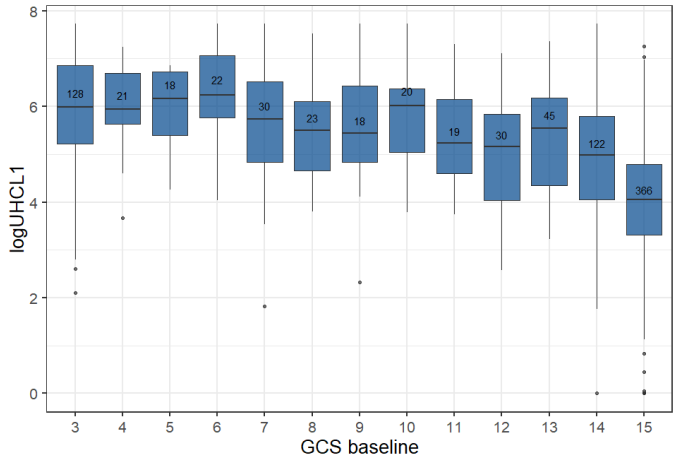
Figure S5: Biomarkers by GCS levels in the CENTER-TBI Core study (n=898)



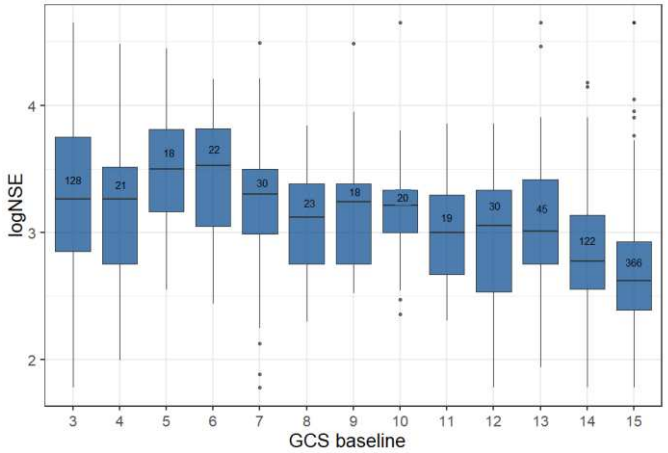
NFL = Neurofilament Light



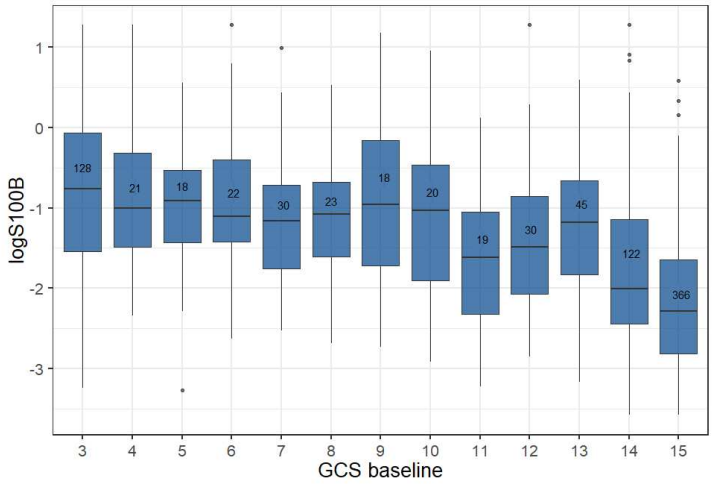
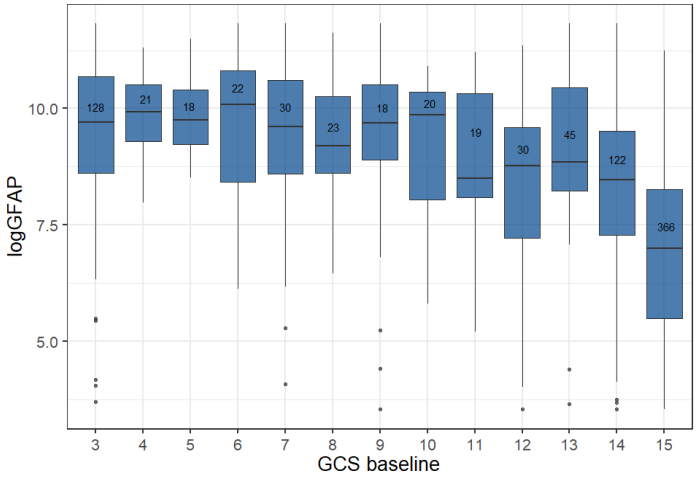
t-TAU = total TAU



UCHL1 = Ubiquitin Carboxy-Terminal Hydrolase L1

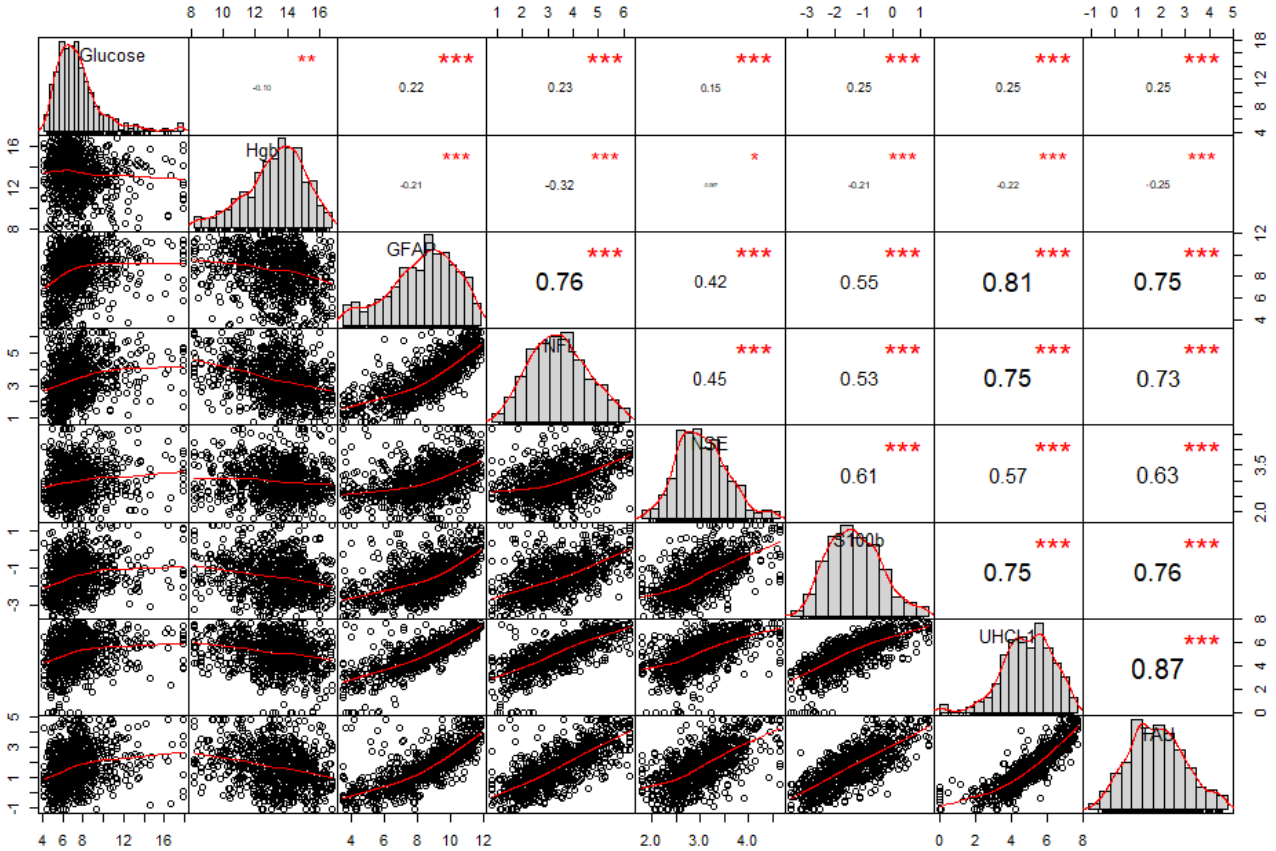


NSE = Neuron-Specific Enolase

	
S100B = S100 calcium-binding protein B	GFAP = Glial Fibrillary Acidic Protein

[#] NSE and S-100B were measured on the e602 module of a Cobas 8000 analyzer (Roche Diagnostics International Ltd· Rotkreuz, Switzerland) in Pecs, Hungary and NF-L, total Tau, GFAP, and UCH-L1 on the Quanterix SIMOA Neurology 4-plex kit (Quanterix, Lexington, MA, USA), at the University of Florida, USA.

Figure S6: Correlation between glucose, hemoglobin, and six biomarkers (GFAP, NFL, NSE, S100B, UHCL1, t-TAU, n=804). Strong correlations were noted, specifically between GFAP, NFL, S100B, UCHL1, and t-TAU (r>0·7)· Only weak correlations were noted between glucose and hemoglobin.



Hgb = Hemoglobin, GFAP = Glial Fibrillary Acidic Protein, NFL = Neurofilament Light, NSE = Neuron-Specific Enolase, S100B = S100 calcium-binding protein B, UCHL1 = Ubiquitin Carboxy-Terminal Hydrolase L1, t-TAU = total TAU· All biomarkers were log transformed.