

# Geriatric Traumatic Brain Injury: Epidemiology, Outcomes, Knowledge Gaps, and Future Directions

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## Abstract

This review of the literature on traumatic brain injury (TBI) in older adults focuses on incident TBI sustained in older adulthood (“geriatric TBI”) rather than on the separate, but related, topic of older adults with a history of earlier-life TBI. We describe the epidemiology of geriatric TBI, the impact of comorbidities and pre-injury function on TBI risk and outcomes, diagnostic testing, management issues, outcomes, and critical directions for future research. The highest incidence of TBI-related emergency department visits, hospitalizations, and deaths occur in older adults. Higher morbidity and mortality rates among older versus younger individuals with TBI may contribute to an assumption of futility about aggressive management of geriatric TBI. However, many older adults with TBI respond well to aggressive management and rehabilitation, suggesting that chronological age and TBI severity alone are inadequate prognostic markers. Yet there are few geriatric-specific TBI guidelines to assist with complex management decisions, and TBI prognostic models do not perform optimally in this population. Major barriers in management of geriatric TBI include under-representation of older adults in TBI research, lack of systematic measurement of pre-injury health that may be a better predictor of outcome and response to treatment than age and TBI severity alone, and lack of geriatric-specific TBI common data elements (CDEs). This review highlights the urgent need to develop more age-inclusive TBI research protocols, geriatric TBI CDEs, geriatric TBI prognostic models, and evidence-based geriatric TBI consensus management guidelines aimed at improving short- and long-term outcomes for the large and growing geriatric TBI population.

**Keywords:** epidemiology; function; geriatric; older adult; traumatic brain injury

## Introduction

**T**RAUMATIC BRAIN INJURY (TBI) is a leading cause of death and disability worldwide. In the United States, 2.8 million people seek medical attention for TBI annually,<sup>1</sup> with an estimated annual cost of over \$76 billion.<sup>2</sup> Sport- and military-related TBI have garnered considerable media attention; however, the highest combined incidence of TBI-related emergency department (ED) visits, hospitalizations, and deaths actually occurs in older adults.<sup>1,3,4</sup> Injury mechanisms, patient characteristics, and biological sequelae of TBI among older adults are distinct from those of younger individuals and require a unique approach to clinical management and research. Epidemiologically, among older adults the most prevalent mechanism of injury is falls, and TBIs occur more commonly in women, whereas for younger individuals most TBIs occur in motor vehicle accidents and in men.<sup>1,5–9</sup> Biologi-

cally, with aging, white matter and vasculature become more susceptible to injury,<sup>10,11</sup> injury response mechanisms such as autophagy are dampened,<sup>12</sup> and prevalence of pre-existing neurological or systemic comorbidities increases.<sup>13</sup>

Unsurprisingly, older adults with TBI experience higher morbidity and mortality,<sup>4,14–16</sup> and slower recovery trajectories<sup>17–20</sup> and have, on average, worse functional, cognitive, and psychosocial outcomes months or years post-injury than do younger patients.<sup>5,17,21–24</sup> Consequently, there is often an assumption of futility surrounding the acute management of these patients. Some centers impose age cutoffs for even offering treatment, such as neurointensive care admission or neurosurgical intervention, for older adults presenting with severe TBI.<sup>25,26</sup> However, a subset of older adults with TBI, including severe TBI, may recover well, suggesting that chronological age and TBI severity alone are inadequate prognostic markers.<sup>27–29</sup> Multiple medical comorbidities

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and cognitive impairment frequently precede TBI among older adults and likely complicate recovery.<sup>13</sup> Yet few studies have assessed the role of pre-existing conditions on outcomes post-TBI in this population, and virtually none have included measures of premorbid function. In fact, older adults, particularly those with pre-existing functional impairment or multiple comorbidities, are often excluded from TBI research altogether.<sup>30</sup> Despite the large and growing epidemic of older adults with incident TBI, there are few to no evidence-based geriatric TBI guidelines to inform complex medical decisions for either acute or long-term management.

This scoping review<sup>31</sup> of the literature on all-severity TBI in older adults focuses on incident TBI sustained in older adulthood (“geriatric TBI”) rather than on the separate, but related, topic of older adults with a history of earlier-life TBI. Whereas most past studies define “older adults” as those 60–65 years of age or older, we chose to use the more inclusive age cutoff of 50–55 years or older that is used in several well-known longitudinal studies of aging<sup>32,33</sup> as well as several past studies of geriatric TBI.<sup>18,20,34–38</sup> We describe the epidemiology of TBI in older adults, the role of comorbidities and baseline function, diagnostic testing, emerging geriatric TBI guidelines and management issues, outcomes, and critical future directions for research.

## Methods

We conducted a scoping review following the methodological framework proposed by Arksey and O’Malley<sup>31</sup> to achieve the broad goals of summarizing current scientific knowledge of geriatric TBI and identifying major research gaps. Briefly, a scoping review is similar to a systematic review, incorporating a systematic approach to reference search, and is therefore less susceptible to bias than a traditional rapid, critical, or expert review.<sup>39</sup> However, given the broader nature of the research question, it generally uses more flexible screening and inclusion criteria and does not involve systematic quality assessment.

In consultation with an experienced medical librarian, we conducted literature searches in PubMed, Web of Science, Biosis Previews, Embase, and PsycINFO to explore six related questions about TBI in the elderly. The PubMed search used the following MeSH terms and keywords: (“brain injuries, traumatic” [MeSH] OR “brain concussion” [MeSH] OR “traumatic brain injury” OR “traumatic brain injuries” OR concussion) AND (“aged, 80 and over” [MeSH] OR elderly or “older adults” or geriatric or elders)) without limiting results by date of publication. Because there are no available MeSH terms to specifically identify adults ages 50 and older, we used a combination of the one available specific MeSH term (“Aged, 80 and over”) and several non-MeSH terms (“elderly,” etc) to identify our target age category. This search returned 9010 citations. We combined this root search with each of six targeted subtopic searches: 1) epidemiology (2435 citations); 2) outcomes (2180 citations); 3) biomarkers (721 citations); 4) neuroimaging (including magnetic resonance imaging [MRI] and positron emission tomography [PET]; 1447 citations); 5) comorbidities (682 citations); and 6) guidelines (176 citations). Subtopic searches were conducted on February 6, 2017, and results were not limited by date of publication. The PubMed search algorithm was then translated to work properly in Web of Science, Biosis Previews, Embase, and PsycINFO by substituting in database-specific controlled vocabulary. These additional database searches yielded the following nonduplicated citations in each subtopic: 1) epidemiology (1446 citations); 2) outcomes (1603 citations); 3) biomarkers (262 citations); 4) neuroimaging (in-

cluding MRI and PET; 1043 citations); 5) comorbidities (352 citations); and 6) guidelines (327 citations).

English-language titles and abstracts were manually screened by the authors (R.C.G., K.D.O., and M.R.M.) for relevance. Priority was given to references originating from PubMed. The vast majority of citations identified were not relevant to geriatric TBI, and therefore >95% of citations were eliminated at this initial stage. Additional articles were identified from governmental sources, for example, the Centers for Disease Control and Prevention (CDC), from consultation with subject-matter experts, and from cited reference searching in PubMed. This scoping review represents a qualitative summary and synthesis of the most relevant literature identified.

## Epidemiology

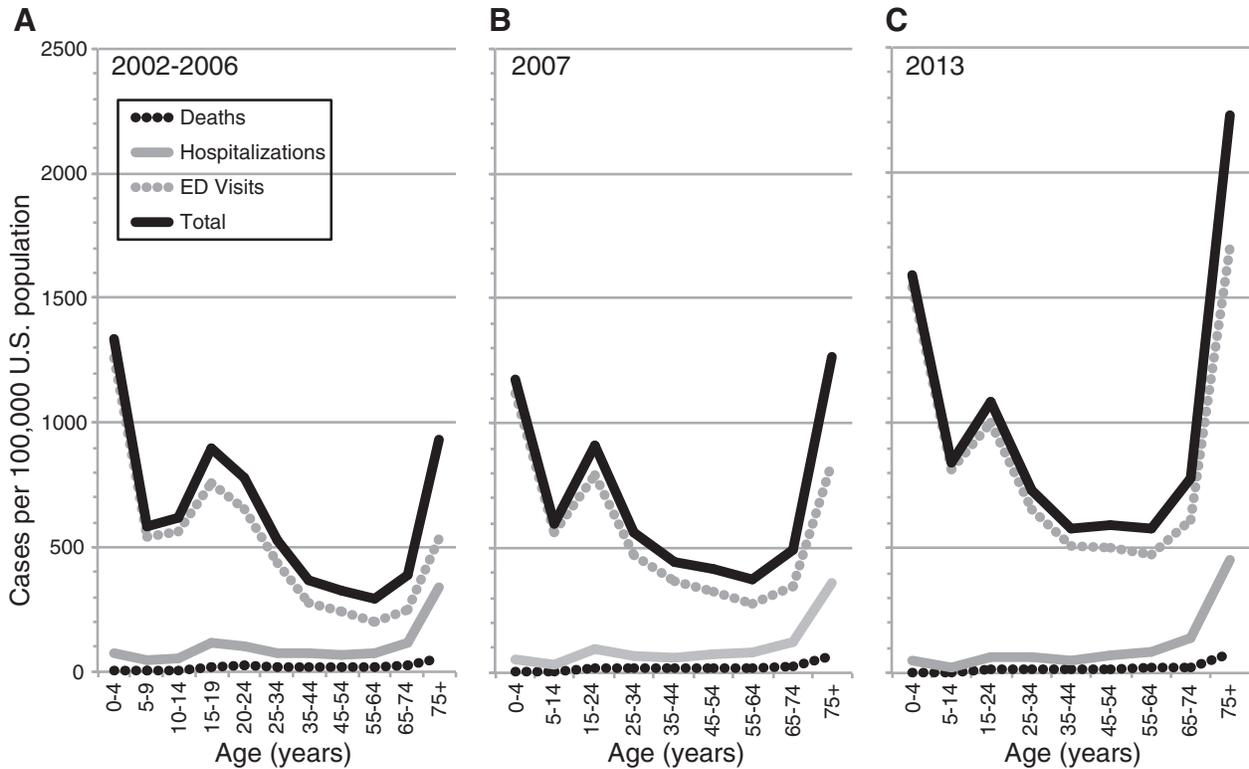
### *Prevalence and incidence*

TBI is extremely common, with a lifetime prevalence of up to 40% among adults.<sup>40</sup> Whereas incidence of TBI peaks three times over the life course—in childhood, adolescence, and older adulthood—the highest incidence of TBI occurs in older adults (Fig. 1). More than 1 in 200 Americans ages 65–74 years and more than 1 in 50 Americans ages ≥75 years experienced a TBI-related ED visit, hospitalization, or death in 2013, with the next highest incidence occurring in children ages 0–4 years (incidence 1,591 in 100,000).<sup>1</sup> In 2013, adults ages ≥75 years accounted for 26.5% of all TBI-related deaths and 31.4% of all TBI-related hospitalizations in the United States. From 2006 to 2008, 800,000 adults ages ≥65 years were evaluated in U.S. EDs for TBI, among whom the average age was 80 years.<sup>41</sup> Incidence of admission to acute inpatient rehabilitation for a primary diagnosis of TBI also increases with age, with the highest incidence occurring among those ages ≥80 years.<sup>5</sup>

Incidence of TBI-related ED visits, hospitalizations, and deaths is increasing among older adults, whereas incidence of TBI-related hospitalizations and deaths is declining among children and adults <55 years of age<sup>42</sup> (Fig. 1). From 2007 to 2013, TBI-related ED visits among those ages ≥75 years doubled and TBI-related hospitalizations increased more than 25%.<sup>1</sup> The rapid rise in TBI-related hospital visits among the oldest segment of the U.S. population exceeded population growth during this time frame.<sup>9</sup> This high and increasing incidence of TBI-related ED visits, hospitalizations, and deaths among older adults has been confirmed in multiple epidemiological studies in individual U.S. states and nation-wide databases<sup>4,43–45</sup> as well as in higher-income countries around the globe including Spain,<sup>46</sup> the United Kingdom (UK),<sup>47</sup> Scotland,<sup>48</sup> the Netherlands,<sup>49</sup> Austria,<sup>50</sup> Finland,<sup>51</sup> Canada,<sup>52–54</sup> and Australia.<sup>7</sup> Despite this high incidence, older adults may be less likely to seek medical attention for TBI<sup>55</sup> and are also less likely to be accurately diagnosed even when medical attention is sought.<sup>56</sup> These findings suggest that TBI incidence among older adults likely exceeds published reports.

### *Mechanisms and demographics*

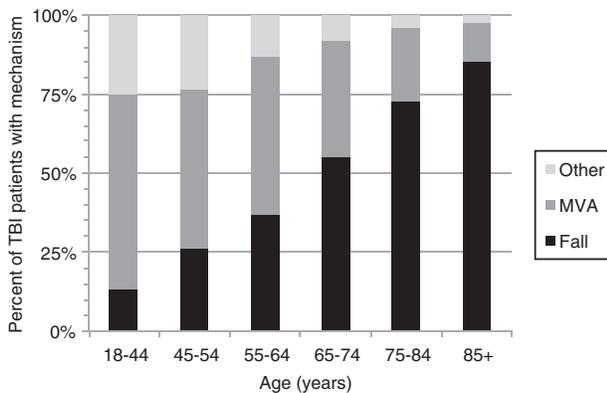
The majority of TBIs sustained by older adults are attributed to low-level or same-level falls from standing height or less,<sup>7,57</sup> even among those requiring surgical treatment of traumatic intracranial hemorrhage (Fig. 2).<sup>58</sup> Mechanisms of TBI are biologically important because fall-related TBIs more commonly result in mass lesions, such as subdural hemorrhage, while the motor vehicle accident-related TBIs experienced by teens and younger adults more commonly result in diffuse axonal injury.<sup>59</sup> Physically active



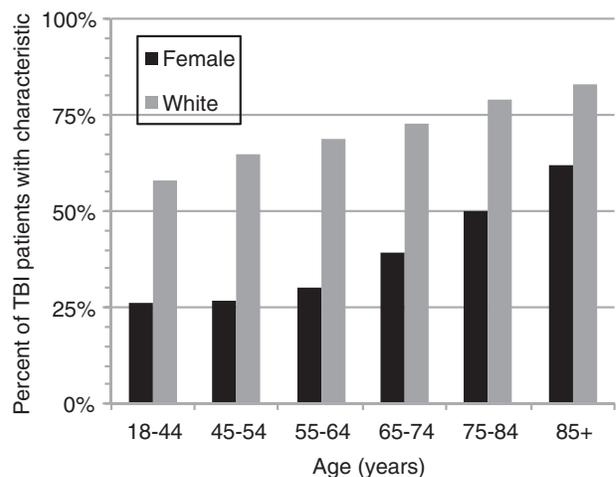
**FIG. 1.** Annual incidence of traumatic brain injury (TBI) emergency department (ED) visits, hospitalizations, and deaths 2002–2013 by age. Annual incidence of TBI-related ED visits, hospitalizations, and deaths per 100,000 U.S. population are shown for the periods 2002–2006 (A), 2007 (B), and 2013 (C). Over time, incidence of TBI has shown the greatest increase among adults  $\geq 75$  years of age, with most of this increase attributed to increased ED visits. Data adapted from the Centers for Disease Control.<sup>1,3</sup>

older adults may be at elevated risk for specific sport-related mechanisms. For example, adults ages 55–64 years have the highest incidence of skiing-related TBI.<sup>60</sup> Bicycle-related injuries, including TBI, in older adults most commonly occur while mounting or dismounting the bicycle.<sup>61</sup> Compared to younger individuals with TBI, older adults are less likely to engage in alcohol or drug abuse.<sup>5</sup> Finally, the majority of the oldest old patients with TBI are female and white (Fig. 3),<sup>9,41,51,56</sup> mirroring U.S. nation-

wide demographics of aging.<sup>62</sup> Although few population-based or multi-center studies have compared the distribution of TBI severity (e.g., mild, moderate, or severe) across age categories, at least one U.S. nationally representative study reported a similar distribution of TBI severity as defined by the Glasgow Coma Scale (GCS) and Abbreviated Injury Scale (AIS) across the age spectrum.<sup>9</sup>



**FIG. 2.** Major mechanisms of traumatic brain injury (TBI) by age (2007–2010). Falls are shown in black; motor vehicle accidents (MVA), in dark gray; and other mechanisms, in light gray. Mechanism of TBI among older adults is predominantly falls whereas mechanism among younger individuals is predominantly MVA.<sup>9</sup>



**FIG. 3.** Sex and race of adults with traumatic brain injury (TBI) by age (2007–2010). The demographics of TBI shift toward increasing prevalence of white race (dark gray bars) and female sex (black bars) with increasing age such that by age 85 years+ the majority of patients with TBI are female.<sup>9</sup>

### Healthcare cost and utilization

Compared to younger patients with TBI, those ages  $\geq 65$  years who seek emergent care are nearly 3 times more likely to receive a head computed tomography (CT) or MRI in the ED setting and 4 times more likely to be admitted to the intensive care unit (ICU), step-down, or surgical unit.<sup>41</sup> In the inpatient rehabilitation setting, an improvement of one point on either the Functional Independence Measure (FIM) or the Disability Rating Scale was associated with double the healthcare expenditures in older versus younger adults.<sup>18</sup> In a large, nation-wide sample of older adults treated in hospitals for TBI,<sup>63</sup> the average annual treatment cost per person ranged from \$73,000 to \$78,000.<sup>64</sup> In this study, older-old patients had significantly lower rates of outpatient injury-related clinic visits and significantly higher rates of rehospitalizations, home healthcare visits, and weekly hours of unpaid care from friends and family compared to younger-old patients, suggesting possible age-related disparities in coordinated care after hospital discharge.<sup>64</sup>

### The Role of Pre-Existing Comorbid Conditions and Baseline Function

Pre-existing conditions are extremely common among older adults with TBI. In a nation-wide study of older adults admitted to UK hospitals for TBI, 11% had pre-existing dementia, 22% had pre-existing hypertension, and 99% had at least one pre-existing medical condition.<sup>47</sup> Those with one pre-existing condition often had additional co-occurring conditions, such as diabetes, cardiovascular disease, pulmonary disease, or renal disease.<sup>65,66</sup> Pre-injury cardiovascular conditions and endocrine disorders are particularly common in the oldest age categories of adults with moderate-severe TBI, with the presence of these conditions occurring up to 5 times more frequently among those  $>75$  years of age compared to those ages 50–54 years.<sup>65</sup>

Pre-existing conditions, including past history of TBI, are risk factors for sustaining a TBI. Among adults  $\geq 65$  years, baseline cerebrovascular disease, depression, and impaired activities of daily living are associated with late-life incident TBI risk.<sup>13</sup> Earlier-life TBI accounts for an estimated 20% of population-attributable risk of late-life TBI.<sup>15</sup> Several additional studies demonstrate higher past-year medical costs among older adults who sustain a TBI (relative to matched uninjured controls)<sup>67</sup> and greater numbers of systemic disease hospital admissions in the years preceding injury compared to those with non-brain injury.<sup>68</sup> This is not surprising, given that falls are the most common cause of TBI in older adults,<sup>1</sup> and older adults who are pre-disposed to falls are more likely to have chronic medical conditions,<sup>8</sup> history of past TBI,<sup>69</sup> medication side effects, visual impairment, cognitive impairment, and balance or gait impairment.<sup>8,70–72</sup>

Pre-existing conditions, including past history of TBI, are associated with worse outcomes post-TBI. In two large, prospective studies, past history of TBI was associated with worse emotional, psychosocial, and behavioral outcomes, including substance use problems, even though those with past TBI had overall less-severe index injuries.<sup>73,74</sup> Greater disease comorbidity at the time of TBI is associated with reduced functional independence at rehabilitation admission,<sup>75</sup> at discharge,<sup>75</sup> and 2–4 years post-injury<sup>76</sup> as well as with increased 1-year mortality.<sup>77</sup> Individuals  $>55$  years of age with TBI who died within 5 years of discharge after inpatient rehabilitation had more comorbid medical conditions and gait instability noted in the hospital records compared to matched survivors.<sup>78</sup> Trauma centers are seeing a greater proportion of elderly patients with more comorbid diseases as the U.S. population ages<sup>79</sup>; these trends, along with improvement in trauma care, have resulted in a

shift in the causes of death after traumatic injury, such that fewer people are dying of injury-related complications whereas more people are dying of complications of pre-existing medical conditions.<sup>80</sup> It is therefore not surprising that self-rated poor health in the year preceding TBI may be more predictive of outcome after mild TBI than injury characteristics in older adults.<sup>81</sup>

The critical importance of pre-morbid functional status in predicting long-term morbidity and mortality in older adults has been established in studies of older hospitalized adults and older adults with hip fracture.<sup>82–85</sup> Several studies of geriatric trauma (not TBI-specific) have demonstrated that incorporating comorbidities, polypharmacy, baseline function, or measures of frailty into prediction models of outcome post-trauma substantially improve their prognostic value.<sup>86,87</sup> In an illustrative case report, Crossley and colleagues elegantly described an 80-year-old woman with normal pre-injury function—defined as complete independence in self-care, financial and household management, and an active and healthy lifestyle—who made an excellent recovery after a severe TBI.<sup>88</sup> Very few studies of outcomes after geriatric TBI, however, have systematically measured pre-TBI functional status<sup>21,64,89–91</sup> and even fewer have assessed the prognostic role of pre-TBI functional status on outcomes.<sup>92,93</sup>

### Initial Clinical Assessment and Diagnostic Studies

#### Clinical assessment

The GCS, although the most widely used clinical assessment to determine TBI severity at the time of initial presentation, may lack the nuance required to accurately assign TBI severity in older adults. Older adults with pre-existing dementia may have an abnormal GCS at baseline,<sup>94</sup> others may have comorbid medical conditions or medication side effects that may complicate accurate diagnosis,<sup>95</sup> and in others the burden/evolution of TBI may not be adequately captured by the initial GCS.<sup>96,97</sup> As an example, age-related atrophy may provide space for an intracranial hemorrhage to expand substantially before leading to clinically apparent signs or symptoms that would be detected by the GCS. Thus, there is an urgent need for objective biomarkers to aid in the diagnosis, management decisions, and recovery monitoring of older adults with TBI, particularly those with pre-existing medical or neurological conditions.

#### Neuroimaging

Head CT is an important diagnostic tool in the acute evaluation, management, and outcome prediction for patients across the age spectrum. CT evidence of neurotrauma both increases with age and is associated with worse outcomes.<sup>36,98,99</sup> The types of neurotrauma observed on head CT differ by age: Prevalence of extradural hematoma declines with age whereas prevalence of midline shift and subdural hematoma increases.<sup>100</sup> Among adults ages  $\geq 65$  years admitted to hospitals with any severity of TBI, up to 45% may have subdural hematoma apparent on head CT.<sup>47</sup> Among adults ages  $\geq 65$  years presenting to the ED with mild TBI (GCS 13–15), 11–21% may have evidence of intracranial trauma (compared with 5% in younger adults).<sup>101–104</sup> Even those with normal GCS (GCS = 15) are at high risk: 17% of adults  $>60$  years of age with a normal GCS had a positive head CT in one large Canadian study,<sup>102</sup> and 57% of adults  $>60$  years of age who were found to have an intracranial hemorrhage on head CT had presented with a normal GCS in a large Swedish study.<sup>101</sup> This dramatically higher prevalence of CT evidence of neurotrauma among older versus younger patients is

hypothesized to result from several factors: age-related changes in vasculature and white matter rendering vessels more vulnerable to rupture and white matter tracts more susceptible to shear injury, weakened musculature in the neck and trunk; such that even ground-level falls are not well braced by the body, pre-existing conditions, and medications such as antithrombotics.<sup>10,11,13</sup>

Structural MRI has been shown to improve prognostic modeling post-TBI by identifying evidence of neurotrauma that may be missed on head CT.<sup>105</sup> Only a few studies have investigated the impact of age on MRI findings in TBI. One prospective study of 98 patients across the spectrum of age and TBI severity that performed MRIs, on average, 2.3 years post-TBI identified an association between older age and both larger lesion volumes and smaller gray matter volumes.<sup>106</sup> Emerging neuroimaging technologies for TBI include advanced structural MRI sequences such as diffusion tensor imaging or 7-Tesla MRI, functional MRI,<sup>107</sup> and a number of PET ligands that bind (with varying specificity) to amyloid-beta, tau, and markers of inflammation.<sup>108,109</sup> Using these emerging technologies in older adults deserves further study. Evidence of tau or amyloid deposition on PET in older adults with TBI, however, will need to be interpreted carefully given evidence from multi-site nonselected autopsy studies that have demonstrated that high-grade amyloid and tau neuropathology increase approximately 10–15% per decade beginning in the sixth decade of life, rising from 1% to 2% among those ages 61–65 years to nearly 40% among those ages 91–95 years.<sup>110</sup>

#### *Emerging proteomic and blood biomarkers*

Recent advances in biochemical assays of serum and cerebrospinal fluid (CSF) have identified a number of promising candidate blood-based and proteomic biomarkers of apoptosis and neuronal injury (neuron-specific enolase, tau, and amyloid-beta 1–42), glial injury (glial fibrillary acidic protein [GFAP], S100B, and excitatory amino acids), demyelination (myelin basic protein), proinflammatory cytokines (interleukins-1, –6, and –8), and gene expression of microRNAs (miR-16, miR-26a).<sup>111</sup> Very few studies have evaluated the impact of aging on the kinetics or clinical performance of serum or CSF-based biomarkers of TBI.<sup>112–117</sup> For example, although serum S100b showed initial promise in identifying low-risk patients who do not require head CT,<sup>118</sup> this biomarker may have reduced specificity among adults ages  $\geq 65$  years.<sup>113</sup> Additional emerging evidence suggests that there may be differences in CSF levels of excitatory amino acids and cytokines in older versus younger patients with TBI that may be independent of TBI severity.<sup>114</sup> Of note, circulating cytokine levels are affected by a range of comorbidities that are common among older adults, including hypertension, diabetes, dementia, Parkinson's disease, and osteoporosis.<sup>119,120</sup> Studies of TBI biomarkers in rodent models have identified compelling differences between aged and younger animals on TBI-associated proteomic signatures,<sup>115</sup> peri-TBI levels and temporal sequences of mRNA expression of microglial (CD11b and ionized calcium binding adaptor molecule 1), and astrocytic (GFAP and S100b) activation markers,<sup>116</sup> and peripheral monocyte recruitment post-TBI.<sup>117</sup>

## **Management**

### *Guidelines*

Older adults with TBI are more likely to experience an interfacility transfer to a level 1 or 2 trauma center compared to younger adults, suggesting higher rates of either inappropriate initial triage

or delayed deterioration necessitating transfer.<sup>121</sup> The GCS is widely used to assign TBI severity, but is poorly predictive of morbidity and mortality in older adults who frequently have better initial GCS scores than younger individuals with the same injury severity.<sup>122</sup> For this reason, researchers in Ohio have been working to develop and validate geriatric trauma-field triage criteria to optimally identify older adults with TBI who require emergent transfer to a trauma center, for example, a GCS cutoff of  $\leq 14$  (vs.  $\leq 13$  for younger individuals).<sup>123–125</sup>

Most, but not all,<sup>126</sup> existing rules and validation studies support the routine use of head CT for all patients  $>60$ <sup>102</sup> or  $>65$  years of age<sup>103,104,127,128</sup> presenting with mild TBI even after rapid return to baseline. The American College of Emergency Physicians recommends considering head CT in all patients ages  $\geq 65$  years who present with TBI, even mild injury without loss of consciousness (LOC), and recommends obtaining a head CT in all patients  $>60$  years of age with TBI and LOC.<sup>129</sup> The Canadian CT Head Rule identifies ages  $\geq 65$  years as a high-risk factor for intracranial trauma needing neurosurgical intervention among patients presenting with TBI and a GCS of 13–15, regardless of LOC.<sup>103</sup> A large Austrian study later confirmed age  $>65$  years as a high-risk factor for CT evidence of neurotrauma, but also identified novel high-risk comorbidities, including history of dementia or ischemic stroke.<sup>128</sup> Further development and validation of geriatric TBI neuroimaging guidelines are therefore critically important.

Efforts are underway to predict which geriatric TBI patients may be managed safely on a standard medical or surgical ward rather than an ICU.<sup>130,131</sup> One Swedish trauma center developed a protocol for geriatric neurosurgical decision making based on pre-injury functional status and predicted 1-year survival.<sup>29</sup> While this center reported favorable outcomes in 41% of patients  $>65$  years of age who underwent craniotomy for acute subdural hemorrhage, further research is needed to determine whether this approach may be overly conservative.<sup>29</sup> According to the Eastern Association for the Surgery of Trauma, clinicians are encouraged to limit further aggressive treatment for older adults with severe TBI who do not improve within 72 h of admission. However, at least one retrospective observational study found that although lack of improvement by 72 h was significantly associated with increased in-hospital mortality, it was not associated with functional status at discharge or 12-month survival among those who survived to discharge.<sup>27</sup>

There remain, however, few to no evidence-based national or international consensus guidelines to inform acute inpatient management or long-term outpatient follow-up of older adults with TBI. This is, in large part, attributed to the paucity of dedicated Class I prospective clinical trials of treatments for older adults with TBI. In the absence of evidence-based guidelines, some centers have proposed strict age cutoffs for offering aggressive treatment such as neurointensive care admission or neurosurgical intervention for older adults with severe TBI,<sup>25,26,132</sup> whereas others have a policy to admit all older adults with any TBI to the neurointensive care unit for serial neurological assessments and head CTs—a practice that may prove overly conservative.<sup>133</sup>

### *Neurocritical care and neurosurgical management issues*

Acute care and prognosis of older adults with moderate-to-severe TBI are particularly challenging as demonstrated by dramatic variability in practice and outcomes across centers (Supplementary Table; see online supplementary material at

<http://www.liebertpub.com/neu>). A few recent observational, largely retrospective studies have assessed the value of various acute neurosurgical interventions including intracranial pressure (ICP) monitoring,<sup>134,135</sup> craniotomy,<sup>136</sup> and decompressive craniectomy<sup>132,136</sup> in older adults with moderate-to-severe TBI. However, these studies may be limited by confounding by indication and other potential sources of bias such as the physician's opinion of a patient's prognosis, which may impact treatment decisions.

Whether ICP monitoring improves outcomes in this population remains controversial, with some studies supporting its use<sup>134</sup> and one study finding no evidence of meaningful benefit.<sup>135</sup> The surprisingly low prevalence of ICP monitoring in the negative study, however, suggests that there may have been unmeasured confounding variables. A single-center study of continuous bedside neuromonitoring data found that although older patients have lower ICP and higher cerebral perfusion pressure compared to younger patients, factors typically associated with better outcomes,<sup>137</sup> they also had worse vascular pressure reactivity and autoregulation compared to younger patients, factors that may contribute to worse outcomes.<sup>137</sup> Together, these findings suggest that although ICP monitoring likely improves outcomes in some older adults, given the tendency for older adults to have lower ICPs on average than younger adults, it is possible that older adults may benefit from the development of geriatric-specific clinical criteria to determine whether ICP monitor placement is appropriate.

There is substantial between-study heterogeneity in outcomes after craniotomy or craniectomy in geriatric TBI.<sup>132,138</sup> The method of surgical intervention may impact outcome as demonstrated by a retrospective cohort study that utilized propensity scores to mitigate confounding by indication; patients who were treated with decompressive craniectomy had worse 6-month Glasgow Outcome Scale (GOS) outcomes compared to those treated with craniotomy.<sup>136</sup>

The contribution of antithrombotic therapies to poor outcomes in older adults with TBI is contested. Some studies have identified increased mortality and worse outcomes for all classes of antithrombotic agents.<sup>139,140</sup> Others report that anticoagulant agents such as warfarin (but not antiplatelet agents) are associated with increased mortality<sup>141</sup> (particularly if warfarin is at a therapeutic level<sup>142</sup>) and need for neurosurgical intervention.<sup>143</sup> Still others have found that early aggressive treatment can mitigate any negative impact of antithrombotics on mortality or outcomes.<sup>144,145</sup> Thus, although antithrombotic therapies may not be associated with worse post-TBI outcomes in a setting in which patients receive rapid and aggressive treatment for hemorrhagic complications and in analyses that adjust for initial TBI severity, it is clear that anticoagulant therapy is associated with worse initial TBI severity, such as acute subdural hemorrhage after relatively minor trauma.<sup>141,142,145,146</sup> This conclusion is further supported by a study of 80 patients (all ages) with acute subdural hemorrhage reporting that initial hematoma volume and GCS are better predictors of hematoma expansion and outcome than age or antithrombotic therapy if patients are rapidly given appropriate agents to reverse coagulopathy.<sup>147</sup> The decision to restart anticoagulants such as warfarin after a TBI in older adults at high risk of thrombotic events or ischemic stroke is complex. One large, retrospective study of over 10,000 Medicare beneficiaries hospitalized for TBI who had been taking warfarin during the month preceding admission reported that restarting warfarin after discharge was associated with a 51% increased risk of all hemorrhagic events and only a 23% reduction in all thrombotic events over the subsequent year. However, when

stroke risk was assessed in isolation, there was a net benefit of a 17% reduction in risk of combined hemorrhagic or ischemic stroke.<sup>148</sup>

## Outcomes

### *The controversial role of age*

It is well established that, on average, older adults with TBI have higher mortality,<sup>4,14–16</sup> slower rates of functional and cognitive recovery,<sup>17–20</sup> and worse functional outcomes post-TBI compared to their younger counterparts.<sup>5,17,21–24</sup> In one of the largest studies to date to investigate the association between age and 6-month functional outcome score on the GOS among 8719 patients with moderate-to-severe TBI contained in the IMPACT database, there was a strikingly linear relationship observed between age and outcome.<sup>149</sup> Thus, some have argued that there is unlikely to be a specific age beyond which outcomes precipitously worsen.<sup>150</sup> Other studies, however, have reported an “inflection point” in the fourth or fifth decade of life at which trauma mortality appears to increase steeply.<sup>151,152</sup> Regardless of the presence or absence of an inflection point, it is clear that a substantial number of older adults with TBI may recover well (Table 1, Table 2, and Supplementary Table; see online supplementary material at <http://www.liebertpub.com/neu>), including some with severe TBI who receive aggressive neurosurgical management.<sup>29,92,138,153–154</sup>

The role of provider attitudes as well as patient and family preferences must also be considered when interpreting outcomes in older adults with TBI, who may be more likely to have care electively withdrawn.<sup>155</sup> The issue of provider attitudes was highlighted in a large UK study of patients with TBI and cerebral contusions, reporting that increasing age was associated with longer delays in obtaining an initial head CT, lower likelihood of being transferred to a neurotrauma center, and lower likelihood of review by a senior (vs. junior) physician.<sup>156</sup> Similar findings suggestive of agism in TBI management decisions were reported in one Scottish study,<sup>157</sup> but a multi-center, prospective U.S. study did not identify any evidence of age-related neurosurgical intervention bias.<sup>91</sup>

### *Outcome assessment*

In the United States, the GOS and the Glasgow Outcome Scale-Extended (GOSE) are the most widely used and widely cited functional outcome measures in TBI clinical research<sup>158</sup> and are included in the National Institute for Neurological Disorders and Stroke TBI Common Data Elements (CDEs).<sup>159</sup> Neither the GOS nor the GOSE were developed or validated in older adults and may not adequately quantify TBI-related functional impairment in a geriatric population, particularly in those with pre-existing functional impairment. For example, a multi-center, prospective study of older adults with severe TBI found that although these patients experienced significant improvement in physical function over 1 year according to the Health Related Quality of Life Measure, this functional improvement was not detected by the GOSE.<sup>160</sup> Additionally, many in the field rely upon the 1998 GOS and GOSE administration and scoring guide by Wilson and colleagues.<sup>161</sup> Yet, even in this comprehensive guide, scoring of patients with pre-injury disability is described as “problematic.”<sup>161</sup> Thus, a patient with severe baseline disability who fully recovers to their severely disabled baseline status may be scored as a GOSE 3 (severe disability) by one study and a GOSE 8 (good recovery) by another study. Additionally, the GOS and GOSE do not systematically

distinguish between effects of brain versus body trauma or between cognitively versus physically mediated function.<sup>161</sup>

We report nearly 40 studies that assessed functional outcome after all-severity or moderate-severe TBI in older adults (Table 2 and Supplementary Table; see online supplementary material at <http://www.liebertpub.com/neu>); functional outcome after mild TBI in older adults is relatively understudied (Table 1). One small U.S. study of 40 adults  $\geq 65$  years of age with mild TBI reported that by 6 months post-injury, 88% had achieved their pre-injury functional status based on the modified FIM.<sup>17</sup> To achieve a perfect score on the modified FIM, however, a patient need only communicate intelligibly and fluently, eat in a “customary manner,” and walk 150 feet.<sup>17</sup> Thus, this instrument may suffer from substantial ceiling effects in a mild TBI population.

There is increasing recognition that the use of the GOS, GOSE, or FIM as the primary endpoint for TBI clinical trials does not adequately capture the complex, multi-dimensional, and evolving nature of TBI, thus historically limiting the success of these trials.<sup>162</sup> To address these limitations, efforts are underway to develop improved TBI endpoints.<sup>163,164</sup> As part of this effort, it will be critically important to either evaluate the performance of existing multi-modal measures in geriatric TBI populations (as was done in this Taiwanese study,<sup>165</sup> these Canadian studies,<sup>166,167</sup> this meta-analysis,<sup>168</sup> and this review/opinion piece<sup>169</sup>) or develop novel multi-modal geriatric-specific TBI endpoints to optimize success of future TBI clinical trials in older adults.

### Mortality

When considering mortality after geriatric TBI, it is important to distinguish between short-term mortality (during initial hospitalization or rehabilitation) and longer-term mortality (over months or years after TBI). Short-term mortality post-TBI is high among older adults, particularly those with severe TBI (Supplementary Table; see online supplementary material at <http://www.liebertpub.com/neu>), with several studies reporting in-hospital mortality rates as high as 70–80% in this population.<sup>98,99</sup> There is, however, substantial variability across centers that may be attributed to a combination of variability in clinical practice and study design. Factors such as aggressive treatment,<sup>138,170</sup> pre-morbid independent function, and good pre-injury health status<sup>37,92,171,172</sup> have been associated with lower short-term mortality among older adults with TBI and most in-hospital deaths in this population occur following decisions to withdraw care.<sup>155,173,174</sup> Other factors associated with short-term mortality in older adults with TBI include older age and CT evidence of brainstem or diencephalic injury, whereas injury mechanism and GCS may be less important predictors.<sup>98</sup> Among older adults who survive the initial hospitalization and rehabilitation period post-TBI; however, several studies have reported that the observed higher mortality among older versus younger individuals may predominantly be accounted for by expected age-related mortality as is observed in the general aging population.<sup>175,176</sup>

### Post-traumatic neurological disorders: Epilepsy, stroke, and neurodegenerative disease

Compared to younger individuals, older adults are at increased risk for post-traumatic epilepsy<sup>177,178</sup> and are more likely to present with delayed rather than early seizures post-TBI.<sup>179</sup> Pre-existing conditions such as Alzheimer’s dementia (AD) further increase the risk of epilepsy in older adults.<sup>180</sup> The choice of drug for both short-term post-traumatic seizure prophylaxis and long-term post-

traumatic epilepsy treatment deserves further study in older adults. First-generation antiepileptic agents such as phenytoin may be suboptimal in older adults because of nonlinear pharmacokinetics, propensity for drug-drug interactions, and cognitive side effects, whereas certain newer agents such as lamotrigine or levetiracetam may be preferable.<sup>181,182</sup>

TBI may be an independent risk factor for both ischemic and hemorrhagic stroke.<sup>183,184</sup> Emerging evidence suggests that initiation of treatment with a selective serotonin reuptake inhibitor (SSRI) among older adults hospitalized for TBI was associated with increased risk of hemorrhagic, but not ischemic, stroke.<sup>185</sup> This finding was further supported by a recent population-based study that identified an association between SSRI initiation and spontaneous hemorrhagic stroke among patients taking oral anti-coagulants.<sup>186</sup> Further research is needed to determine the mechanism of post-TBI stroke and SSRI-associated hemorrhage in order to inform safe management of post-TBI depression (which is common and undertreated in older adults<sup>187</sup>) as well as optimal post-TBI stroke prevention strategies.

Although TBI is now a well-established risk factor for dementia and Parkinson’s disease,<sup>188–191</sup> few past studies have assessed risk of dementia or PD specifically after geriatric TBI (e.g., TBI sustained in the fifth decade or beyond).<sup>34,35,192–194</sup> One small, prospective study of falls and risk of dementia among individuals ages  $\geq 70$  years concluded that fall-related TBI was associated with earlier onset of dementia and that presence of an apolipoprotein E epsilon 4 allele acted synergistically with fall-related TBI to further increase risk of earlier onset of dementia.<sup>192</sup> An important methodological concern in epidemiological studies assessing risk of a neurodegenerative disease after geriatric TBI is the possibility of reverse-causation—that the patient fell and sustained a TBI because of early symptoms of a neurodegenerative disease rather than the reverse. This concern was highlighted by a population-based Danish study reporting that the association between TBI and PD was almost entirely attributed to fall-related TBIs sustained within the 3 months preceding initial PD diagnosis.<sup>194</sup> To mitigate this potential for reverse causation, two large studies using California-wide data from the Healthcare Cost and Utilization Project compared risk of dementia and PD in adults ages  $\geq 55$  years at least 1 year after sustaining a TBI versus fracture. In these studies, incident geriatric TBI was associated with a 44% increased risk of PD and a 26% increased risk for dementia over the subsequent 5–7 years. Even mild TBI was associated with a 24% increased risk for PD for those ages  $\geq 55$  years and a 21–25% increased risk for dementia among those ages  $\geq 65$  years (but not for those ages 55–64).<sup>34,35</sup>

Repeated TBI in older adults may be associated with greater risk for neurodegenerative outcomes than single TBI.<sup>34</sup> Repeated concussive and subconcussive injuries have been associated with chronic traumatic encephalopathy (CTE), a unique degenerative tauopathy, primarily described among contact-sport athletes, blast-exposed military personnel, and victims of domestic violence.<sup>195–197</sup> Whether CTE may result from repeated fall-related TBIs or repeated fall-related subconcussive injuries in older adults is unknown. However, a case series of 139 cases of autopsy-proven multiple system atrophy (MSA)—a rare degenerative movement disorder that causes dysautonomia, parkinsonism, and cerebellar ataxia—identified CTE pathology in 8 cases (6%). Of these 8 cases, only 4 had a history of contact sports generating the hypothesis that repeated falls attributed to MSA may have precipitated the CTE pathology.<sup>198</sup> An analysis of over 1700 brains from the Mayo Clinic brain bank, however, did not identify any cases of CTE in patients exposed to a single fall-related TBI.<sup>199</sup>

TABLE 1. STUDIES ASSESSING MORTALITY OR FUNCTION AFTER GERIATRIC MILD TBI

<i>Study; design</i>	<i>Site</i>	<i>N</i>	<i>Age</i>	<i>Population</i>	<i>Time points</i>	<i>Functional Outcomes</i>	<i>Compared with young?</i>	<i>Predictors</i>
Kristman and colleagues I, 2016 <sup>17</sup> ; Pro	Multi-center, Canada	49	≥65	Mild TBI discharged from ED	6mo	6mo GOSE 5-4: 80% <4: 20%	N	Pre-TBI health status, depression, fatigue, and poor expectations for recovery predicted worse outcome
Cheng and colleagues, 2014 <sup>23</sup> ; Retro	Nation-wide health insurance claims database, Taiwan	5997	≥65	Mild TBI	Variable, up to 5y	Mortality 14.5%	N	Although mortality percent higher in controls without mild TBI (N=84,117; mortality 19.7%) adjusted survival models identified increased risk of death after mild TBI compared with controls without TBI.
McIntyre and colleagues et al, 2013 <sup>14</sup> ; Retro	Meta-analysis 1989-2011	6 studies	≥60	Mild TBI (GCS 13-15)	Variable, up to 6mo	Mortality 12.3%	N	—
McIntyre and colleagues, 2013 <sup>15</sup> ; Retro	Meta-analysis 1986-2008	5 studies	≥60	Mild TBI (GCS 13-15)	12mo	GOS 5-4: 80.5% 3-2: 7.0%	N	—
Flaada and colleagues, 2007 <sup>175</sup> ; Retro	Population-based, Olmsted County, U.S.	99	≥65	Mild TBI	6mo, 10y	1 (mortality): 10.7% Mortality 6mo: 9.1% 10y: 51.5%	Y (N=1173)	Mortality among survivors >6mo not greater than predicted for normal aging (survivors to 6 months should expect to have normal life span for age). Relative increases in TBI-related mortality with increasing age are not greater than expected compared with population-based mortality estimates.
LeBlanc and colleagues, 2006 <sup>6</sup> ; Retro	Single-center, Canada	476	≥60	Mild TBI	Hospital discharge	In-hospital mortality 8.4% 44.8% discharged to home	Y (N=1003)	—
Mosenthal and colleagues, 2004 <sup>17</sup> ; Pro	Multi-center, U.S.	40	≥65	Mild TBI (GCS 13-15) evaluated at a trauma center who survived to hospital discharge	Hospital discharge, 6mo	Hospital discharge Mean modified FIM 10.4 68% independent GOS 5: 63% GOS 4: 14% GOS 3: 23% 6mo Mean modified FIM 11.0	Y (N=142)	—

This table summarizes outcomes data for identified studies that report group-level mortality or functional outcomes after geriatric TBI. Whereas primary outcomes reported in each study may differ from those reported in this table, data displayed here were chosen to optimize direct comparison across studies.  
ED, emergency department; FIM, functional independence measure; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; GOSE, Glasgow Outcome Scale-Extended; Pro, prospective; Retro, retrospective; TBI, traumatic brain injury.

TABLE 2. STUDIES ASSESSING MORTALITY OR FUNCTION AFTER GERIATRIC ALL-SEVERITY TBI

<i>Study; design</i>	<i>Site</i>	<i>Geriatric TBI N</i>	<i>Age</i>	<i>Population</i>	<i>Time points</i>	<i>Functional Outcomes</i>	<i>Comparison to younger TBI?</i>	<i>Predictors</i>
Peck and colleagues, 2014 <sup>37</sup> ; Retro	Single-center, U.S.	353	≥55	TBI who survived initial hospitalization	6mo, 12mo	Mortality 6mo 10.6% 12mo 13.4%	N	Older age, pre-injury anticoagulant use, more comorbidities, discharge to long-term care facility, and severe disability (but <i>not</i> TBI severity) predicted post-discharge mortality
McIntyre and colleagues, 2013 <sup>14</sup> ; Retro	Meta-analysis 1989–2011	22 studies	≥60	All-severity TBI	Variable, up to 10y	Mortality 38.3%	N	—
Dijkers and colleagues, 2013 <sup>216</sup> ; Pro	Multi-center, U.S.	339	≥65	All-severity TBI admitted to inpatient rehabilitation	Inpatient rehab admission, discharge and 3 and 9mo post-discharge	Detailed motor and cognitive FIM scores at admission, discharge, 3mo, and 9mo by 10-year age categories Mortality 3mo: ~5% 9mo: ~13% ~70% discharged to home	Y (N=1078)	—
Graham and colleagues, 2010 <sup>205</sup> ; Retro	Multi-center (Uniform Data System for Medical Rehabilitation), U.S.	18,413	≥65	TBI admitted to inpatient rehabilitation, living at home pre-injury	Inpatient rehab admission and discharge	FIM (mean) Admission: 56 ± 19 Discharge: 81 ± 23 66% discharged to home	N	Older age predicted worse functional outcome
Bhullar and colleagues, 2010 <sup>235</sup> ; Retro	Single-center, U.S.	328	≥65	All-severity TBI evaluated at trauma center	Variable, up to 3y	Mortality Age 65–80y: 21% Age >80y: 6%	Y (N=2041)	Trend toward lower mortality in oldest old (>80y) compared to younger old
Yap and colleagues, 2008 <sup>38</sup> ; Retro	Single-center, Singapore	52	≥55	All-severity TBI admitted to inpatient rehabilitation (31% severe by GCS <9; 90% severe by PTA >1 week)	Inpatient rehab admission, discharge, 6mo	GOS discharge 5: 0% 4: 3.8% 3: 92.3% 2: 1.9% 1 (mortality): 1.9% GOS 6mo 5: 3.8% 4: 17.3% 3: 63.5% 2: 1.9% 1 (mortality): 3.8% 90% discharged to home	N	—

(continued)

TABLE 2. (CONTINUED)

<i>Study; design</i>	<i>Site</i>	<i>Geriatric TBI N</i>	<i>Age</i>	<i>Population</i>	<i>Time points</i>	<i>Functional Outcomes</i>	<i>Comparison to younger TBI?</i>	<i>Predictors</i>
Chang and colleagues, 2008 <sup>217</sup> ; Retro	Nationally representative sample (Uniform Data System for Medical Rehabilitation), U.S.	9240	≥65	All-severity TBI admitted to inpatient rehabilitation	Inpatient rehab discharge	FIM (mean ±SD) White: 82 ±25 Black: 75 ±27 Hispanic: 80 ±26 Discharged to home White: 62% Black: 65% Hispanic: 71% FIM (mean ±SD) Admission: 54 ±23 Discharge: 88 ±24 DRS (mean ±SD) Admission: 12 ±5 Discharge: 7 ±4 81% discharged to home Mortality 24%	N	White race predicted better FIM at discharge but less likely to be discharged to home compared to black or Hispanic
Frankel and colleagues, 2006 <sup>20</sup> ; Retro	TBI Model Systems Database, U.S.	267	≥55	All-severity TBI admitted to inpatient rehabilitation	Inpatient rehab admission and discharge	FIM %abnormal Expression: 17% Feeding: 34% Locomotion: 36% 54% discharged to extended care GOSE 5: 20% Mortality: ~30% Achieved pre-injury living situation: ~45%	Y (N=267)	—
Susman and colleagues, 2002 <sup>236</sup> ; Retro	New York State Trauma Registry, U.S.	3244	≥65	All-severity TBI evaluated at a trauma center	Hospital discharge	FIM (mean ±SD) Admission: 52 ±25 Discharge: 91 ±28 DRS (mean ±SD) Admission: 14 ±5 Discharge: 7 ±4 82% discharged to community setting	Y (N=8528)	—
Rothweiler and colleagues, 1998 <sup>97</sup> ; Pro	Single-center, U.S.	25	≥60	All-severity TBI admitted to trauma center who survived 1 month	1y		Y (N=386)	—
Cifu and colleague, 1996 <sup>18</sup> ; Pro	Multi-center (TBI Model Systems), U.S.	50	≥55	All-severity TBI admitted to inpatient rehab (mean ±SD GCS 10 ±4)	Inpatient rehab admission and discharge		Y (N=50)	—

This table summarizes outcomes data for identified studies that report group-level mortality or functional outcomes after geriatric TBI. Whereas primary outcomes reported in each study may differ from those reported in this table, data displayed here were chosen to optimize direct comparison across studies.

DRS, disability rating scale; IVH, intraventricular hemorrhage; ICU, intensive care unit; PTA, post-traumatic amnesia; SD, standard deviation; TBI, traumatic brain injury. Other abbreviations per Table 1.

### *Other chronic psychosocial and cognitive impairments*

Several studies have assessed psychosocial sequelae after geriatric TBI.<sup>24,200–203</sup> Based on a systematic review of post-TBI depression, prevalence of depression is 1.8–8.9% in older community-dwelling adults, 25% in skilled nursing facilities, and 21–37% among older adults with TBI.<sup>201</sup> TBI in older adults has been associated with 11% increased risk of new-onset depression and 50% increased risk of new-onset PTSD.<sup>204</sup> Risk of depression among older adults hospitalized for TBI may be highest immediately after discharge and then decline over the subsequent 12 months.<sup>202</sup> Whereas this reduction in incident depression with increasing time post-injury may be explained by declining rates of post-TBI longitudinal follow-up and resultant ascertainment bias, at least one study has found that depressive symptoms decline over time post-injury only among older, and not younger, adults.<sup>203</sup> Similarly, a small study of 26 older adults with mild TBI found that, compared to younger patients, older adults reported less psychosocial impairment, psychological distress, and physical symptoms 1 month after their TBI, but these findings were largely mediated by employment status.<sup>24</sup> This finding suggests either that older adults are less prone to some of the psychosocial sequelae of mild TBI or that the outcome assessments capturing psychosocial sequelae of TBI are less sensitive among retirees. Together, these findings suggest that careful screening for mood symptoms among older adults with TBI is important at any time post-injury, but particularly within the first few months to years post-injury when risk and symptom burden may be highest.

Cognitive symptoms and impairment after TBI in older adults are common.<sup>205</sup> Just as in younger patients, prevalence and severity of cognitive sequelae in older adults tends to increase with increasing TBI severity.<sup>206</sup> Older adults with TBI, however, experience slower recovery of cognitive function during rehabilitation<sup>18</sup> and over the year after TBI compared to younger patients.<sup>19</sup> Most studies of cross-sectional cognitive outcomes after TBI have reported that older patients have worse cognitive outcomes compared to younger patients.<sup>207</sup> The few studies that have adjusted for expected age-related decline in cognitive function, however, have reported that older adults may have equivalent or even better cognitive outcomes compared to younger individuals with TBI.<sup>207</sup> This compelling finding highlights the importance, as in the evaluation of post-TBI mortality described above, of accounting for expected age-related changes that are unrelated to the injury when comparing outcomes across age categories. Other important modifiers of cognitive outcome in older adults with TBI include pre-injury factors, such as pre-existing comorbidities that may be independently associated with worse cognitive function, as well as the deleterious cognitive impact of trauma and hospitalization more generally, versus the specific impact of TBI. For example, one small study of mild TBI in older adults reported that although 3-month cognitive outcomes were worse among those with mild TBI compared to community-based controls, outcomes were equivalent to orthopedic controls,<sup>208</sup> suggesting that cognitive impairment after mild TBI in older adults may be partially attributed to overall trauma or predisposition to injury.<sup>208</sup>

### *Prognostic models*

As the global incidence of geriatric TBI continues to rise, the need for geriatric TBI prognostic models has become increasingly urgent. Recently two prognostic models have incorporated age as well as clinical and CT indicators of TBI severity and have subsequently each been studied in large, population-based samples of older adults with TBI. The CRASH-CT prognostic model is a

predictor of 14-day mortality and 6-month unfavorable outcome on the GOS and includes only variables of age, GCS, pupil reactivity, extracranial injury, and evidence of trauma on head CT.<sup>209</sup> The model does not take into account baseline comorbidities or pre-injury function. The model showed adequate discrimination and calibration in older adults with all-severity TBI (ages 65–84 years) in a U.S. study,<sup>210</sup> but performed very poorly with dramatic over-prediction of mortality (observed 50%; predicted 81%) and unfavorable outcome (observed 72%; predicted 95%) in older adults with severe TBI (ages 65–92 years) in a Norwegian study.<sup>211</sup> The IMPACT prognostic model predicts 6-month mortality and unfavorable outcome on the GOS.<sup>212,213</sup> The IMPACT model includes age, GCS, pupillary reactivity, hypoxia, hypotension, CT evidence of trauma, and blood glucose and hemoglobin levels, but, again, does not include baseline comorbidities (other than those captured by baseline glucose and hemoglobin) or pre-injury function. It showed adequate discrimination, but poor calibration, among older adults (ages 65–84 years) with evidence of substantial under-prediction of mortality.<sup>214</sup> The poor performance of these models in older adults with TBI is not surprising given that the development cohort for both the CRASH-CT and IMPACT models consisted of pooled trials and observational cohort studies that largely excluded older adults with pre-existing comorbidities. Further studies are now needed to determine whether incorporating comorbidities, polypharmacy, baseline function, or measures of frailty into these models will improve their prognostic value, as has already been demonstrated for geriatric trauma outcome prediction models.<sup>86,87</sup>

### **Rehabilitation**

There is substantial evidence that intensive inpatient rehabilitation greatly benefits older adults with TBI,<sup>215</sup> with the majority showing functional gains and achieving discharge to home.<sup>38,205</sup> Although functional gains are often slower in older versus younger individuals, necessitating longer lengths of stay, at least one study from the TBI Model Systems database found that overall net functional gains did not significantly differ between older versus younger patients after accounting for TBI severity.<sup>20</sup> It is therefore concerning that a multi-center study of nearly 1500 patients admitted to nine inpatient rehabilitation hospitals reported that adults ages  $\geq 65$  years received less intensive rehabilitation services (reflected both in shorter length of stay and also fewer hours of therapy per day) than younger patients and regained less functional ability both during and after inpatient rehabilitation.<sup>216</sup> Race and ethnicity—or associated social factors—may play a role in discharge destination, with discharge to home being more likely among older black and Hispanic adults compared to older white adults.<sup>217</sup> There is an emerging literature on best neurerehabilitation practices for older adults with acquired brain injury including stroke and TBI. A key goal of rehabilitation in this population is the removal of “excess disability,” for example, depression, insomnia, pain, and social instability, that may complicate recovery.<sup>215</sup>

### **Future Directions for Research**

Although research on geriatric TBI has expanded in recent years, older adults are severely under-represented in TBI research<sup>218</sup> and important knowledge gaps remain. This under-representation may be attributed to overly restrictive inclusion/exclusion criteria as well as patient factors.<sup>219–221</sup> Although the study of “pure” TBI may be preferable in some observational studies or clinical trials, strict exclusion criteria based on past medical history systematically excludes older adults<sup>222</sup> and unrepresentative study samples have and will

result in a biased and incomplete understanding of TBI outcomes for older adults.<sup>223,224</sup> Further, lack of systematic measurement of pre-injury health and functional status may confound attempts to develop prognostic models in geriatric TBI. Yet, few past studies have measured pre-TBI functional status.<sup>21,90</sup> Rather than treating comorbidities and poor baseline function as detractors from TBI-focused clinical research, heterogeneity of samples could be harnessed to improve power as described by the IMPACT investigators.<sup>221</sup>

Concurrent with the need to increase representation of older adults in TBI research, there is an urgent need to develop geriatric TBI CDEs to encourage a systematic approach to measuring pre-injury comorbidities, preinjury functional status, and geriatric-specific imaging and proteomic biomarkers, and improved prognostic models. This information is necessary to develop evidence-based geriatric TBI treatments and consensus management guidelines, including targeted fall prevention strategies.<sup>225</sup> Current TBI CDEs, such as the GCS or GOSE, may need to be modified (as has already been done for pediatric TBI<sup>226–228</sup>); existing validated measures may be borrowed from other disciplines such as geriatric medicine, trauma surgery, or neurology; and some measures may need to be developed and validated *de novo*.

Last, TBI is now a well-established risk factor for neurodegenerative diseases of aging, including AD and PD, but mechanisms are poorly understood. Geriatric TBI presents an opportunity to understand the biological basis for the association between TBI and neurodegenerative disease in a patient population already at elevated risk for aging-related neurodegeneration. Prospective human studies of post-TBI neurodegeneration are challenging given the often decades-long delay between TBI exposure and neurodegenerative disease onset. By studying geriatric TBI, this delay is substantially shorter and may allow for novel insights into links between TBI and neurodegeneration that will directly inform targeted treatment and prevention of post-TBI neurodegenerative diseases among survivors of TBI across the age spectrum.

## Conclusions

The world's population is aging and growing. The number of older adults presenting to EDs and being admitted to neuro-ICUs for management of TBI is expected to continue to increase in the coming years. There is an urgent need to develop better geriatric-specific prognostic models<sup>210,214,229</sup> and evidence-based geriatric TBI treatments and management guidelines to identify patients who would benefit most from aggressive versus conservative management and to optimally tailor treatment, rehabilitation, and prevention strategies. The first steps will involve designing more inclusive studies of older adults with TBI that incorporate core geriatric research principles, such as avoiding age cutoffs (masquerading as exclusion criteria for comorbidities) and incorporating measurements of pre-injury function, comorbidities, and frailty, which may prove more predictive of outcome after geriatric TBI than numerical age and trauma severity alone. The next critical steps will be development of geriatric-specific TBI CDEs, including geriatric functional assessments, tailored neuroimaging protocols, and validated biomarkers. Only then will we be able to improve diagnosis, clinical care, recovery monitoring, clinical trial endpoints, and eventually short- and long-term outcomes in the large and growing geriatric TBI population.

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## References

1. Taylor, C.A., Bell, J.M., Breiding, M.J., and Xu, L. (2017). Traumatic Brain Injury-Related Emergency Department Visits, Hospitalizations, and Deaths—United States, 2007 and 2013. Morbidity and mortality weekly report. *MMWR Surveill. Summ.* 66, 1–16.
2. Centers for Disease Control and Prevention (CDC). (2013). CDC grand rounds: reducing severe traumatic brain injury in the United States. *MMWR Morb. Mortal. Wkly. Rep.* 62, 549–552.
3. Faul, M., Xu, L., Wald, M.M., Coronado, V., and Dellinger, A.M. (2010). Traumatic Brain Injury in the United States: National Estimates of Prevalence and Incidence, 2002–2006. *Injury Prev.* 16, A268–A268.
4. Ramanathan, D.M., McWilliams, N., Schatz, P., and Hillary, F.G. (2012). Epidemiological shifts in elderly traumatic brain injury: 18-year trends in Pennsylvania. *J. Neurotrauma* 29, 1371–1378.
5. Cuthbert, J.P., Harrison-Felix, C., Corrigan, J.D., Kreider, S., Bell, J.M., Coronado, V.G., and Whiteneck, G.G. (2015). Epidemiology of adults receiving acute inpatient rehabilitation for a primary diagnosis of traumatic brain injury in the United States. *J. Head Trauma Rehabil.* 30, 122–135.
6. LeBlanc, J., de Guise, E., Gosselin, N., and Feys, M. (2006). Comparison of functional outcome following acute care in young, middle-aged and elderly patients with traumatic brain injury. *Brain Inj.* 20, 779–790.
7. Harvey, L.A., and Close, J.C.T. (2012). Traumatic brain injury in older adults: characteristics, causes and consequences. *Injury* 43, 1821–1826.
8. Coronado, V.G., Thomas, K.E., Sattin, R.W., and Johnson, R.L. (2005). The CDC traumatic brain injury surveillance system: characteristics of persons aged 65 years and older hospitalized with a TBI. *J. Head Trauma Rehabil.* 20, 215–228.
9. Dams-O'Connor, K., Cuthbert, J.P., Whyte, J., Corrigan, J.D., Faul, M., and Harrison-Felix, C. (2013). Traumatic brain injury among older adults at level I and II trauma centers. *J. Neurotrauma* 30, 2001–2013.
10. Liu, H., Yang, Y., Xia, Y., Zhu, W., Leak, R.K., Wei, Z., Wang, J., and Hu, X. (2017). Aging of cerebral white matter. *Ageing Res. Rev.* 34, 64–76.
11. Ikonovic, M.D., Mi, Z., and Abrahamson, E.E. (2017). Disordered APP metabolism and neurovasculature in trauma and aging: combined risks for chronic neurodegenerative disorders. *Ageing Res. Rev.* 34, 51–63.
12. Yin, Y., Sun, G., Li, E., Kiselyov, K., and Sun, D. (2017). ER stress and impaired autophagy flux in neuronal degeneration and brain injury. *Ageing Res. Rev.* 34, 3–14.
13. Dams-O'Connor, K., Gibbons, L.E., Landau, A., Larson, E.B., and Crane, P.K. (2016). Health Problems Precede Traumatic Brain Injury in Older Adults. *J. Am. Geriatr. Soc.* 64, 844–848.
14. McIntyre, A., Mehta, S., Aubut, J., Dijkers, M., and Teasell, R.W. (2013). Mortality among older adults after a traumatic brain injury: a meta-analysis. *Brain Inj.* 27, 31–40.
15. Dams-O'Connor, K., Gibbons, L.E., Bowen, J.D., McCurry, S.M., Larson, E.B., and Crane, P.K. (2013). Risk for late-life re-injury, dementia and death among individuals with traumatic brain injury: a population-based study. *J. Neurol. Neurosurg. Psychiatry* 84, 177–182.
16. Coronado, V.G., Thomas, K.E., Sattin, R.W., and Johnson, R.L. (2005). The CDC traumatic brain injury surveillance system: characteristics of persons aged 65 years and older hospitalized with a TBI. *J. Head Trauma Rehabil.* 20, 215–228.

17. Mosenthal, A.C., Livingston, D.H., Lavery, R.F., Knudson, M.M., Lee, S., Morabito, D., Manley, G.T., Nathens, A., Jurkovich, G., Hoyt, D.B., and Coimbra, R. (2004). The effect of age on functional outcome in mild traumatic brain injury: 6-month report of a prospective multicenter trial. *J. Trauma* 56, 1042–1048.
18. Cifu, D.X., Kreutzer, J.S., Marwitz, J.H., Rosenthal, M., Englander, J., and High, W. (1996). Functional outcomes of older adults with traumatic brain injury: a prospective, multicenter analysis. *Arch. Phys. Med. Rehabil.* 77, 883–888.
19. Green, R.E., Colella, B., Christensen, B., Johns, K., Frasca, D., Bayley, M., and Monette, G. (2008). Examining moderators of cognitive recovery trajectories after moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S16–S24.
20. Frankel, J.E., Marwitz, J.H., Cifu, D.X., Kreutzer, J.S., Englander, J., and Rosenthal, M. (2006). A follow-up study of older adults with traumatic brain injury: taking into account decreasing length of stay. *Arch. Phys. Med. Rehabil.* 87, 57–62.
21. Thompson, H.J., McCormick, W.C., and Kagan, S.H. (2006). Traumatic brain injury in older adults: epidemiology, outcomes, and future implications. *J. Am. Geriatr. Soc.* 54, 1590–1595.
22. Thompson, H.J., Dikmen, S., and Temkin, N. (2012). Prevalence of comorbidity and its association with traumatic brain injury and outcomes in older adults. *Res. Gerontol. Nurs.* 5, 17–24.
23. Stocchetti, N., Paterno, R., Citerio, G., Beretta, L., and Colombo, A. (2012). Traumatic brain injury in an aging population. *J. Neurotrauma* 29, 1119–1125.
24. Rapoport, M.J., and Feinstein, A. (2001). Age and functioning after mild traumatic brain injury: the acute picture. *Brain Inj.* 15, 857–864.
25. Hernesniemi, J. (1979). Outcome following head injuries in the aged. *Acta Neurochir.* 49, 67–79.
26. Petridis, A.K., Dorner, L., Doukas, A., Eifrig, S., Barth, H., and Mehdorn, M. (2009). Acute subdural hematoma in the elderly; clinical and CT factors influencing the surgical treatment decision. *Cent. Eur. Neurosurg.* 70, 73–78.
27. Lilley, E.J., Williams, K.J., Schneider, E.B., Hammouda, K., Salim, A., Haider, A.H., and Cooper, Z. (2016). Intensity of treatment, end-of-life care, and mortality for older patients with severe traumatic brain injury. *J. Trauma Acute Care Surg.* 80, 998–1004.
28. De Bonis, P., Pompucci, A., Mangiola, A., D'Alessandris, Q.G., Rigante, L., and Anile, C. (2010). Decompressive craniectomy for the treatment of traumatic brain injury: does an age limit exist? *J. Neurosurg.* 112, 1150–1153.
29. Taussky, P., Hidalgo, E.T., Landolt, H., and Fandino, J. (2012). Age and salvageability: analysis of outcome of patients older than 65 years undergoing craniotomy for acute traumatic subdural hematoma. *World Neurosurg.* 78, 306–311.
30. Isokuortti, H.T., Iverson, G.L., Kataja, A., Brander, A., Ohman, J., and Luoto, T.M. (2016). Who gets head trauma or recruited in mild traumatic brain injury research? *J. Neurotrauma.* 33, 232–241.
31. Arksey, H., and O'Malley, L. (2005). Scoping studies: towards a methodological framework. *Int. J. Soc. Res. Methodol.* 8, 19–32.
32. Heeringa, S.G., and Connor, J. (1995). Technical Description of the Health and Retirement Study Sample Design. Institute for Social Research, University of Michigan: Ann Arbor, Michigan.
33. Kearney, P.M., Cronin, H., O'Regan, C., Kamiya, Y., Savva, G.M., Whelan, B., and Kenny, R. (2011). Cohort profile: the Irish Longitudinal Study on Ageing. *Int. J. Epidemiol.* 40, 877–884.
34. Gardner, R.C., Burke, J.F., Nettiksimmons, J., Goldman, S., Tanner, C.M., and Yaffe, K. (2015). Traumatic brain injury in later life increases risk for Parkinson disease. *Ann. Neurol.* 77, 987–995.
35. Gardner, R.C., Burke, J.F., Nettiksimmons, J., Kaup, A., Barnes, D.E., and Yaffe, K. (2014). Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity. *JAMA Neurol.* 71, 1490–1497.
36. Vollmer, D.G., Torner, J.C., Jane, J.A., Sadovnic, B., Charlebois, D., Eisenberg, H.M., Foulkes, M.A., Marmarou, A., and Marshall, L.F. (1991). Age and outcome following traumatic coma: why do older patients fare worse? *J. Neurosurg.* 75, S37–S49.
37. Peck, K.A., Calvo, R.Y., Sise, C.B., Johnson, J., Yen, J.W., Sise, M.J., Dunne, C.E., Badiee, J., Shackford, S.R., and Lobatz, M.A. (2014). Death after discharge: predictors of mortality in older brain-injured patients. *J. Trauma Acute Care Surg.* 77, 978–983.
38. Yap, S.G.M., and Chua, K.S.G. (2008). Rehabilitation outcomes in elderly patients with traumatic brain injury in Singapore. *J. Head Trauma Rehabil.* 23, 158–163.
39. Grant, M.J., and Booth, A. (2009). A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Info. Libr. J.* 26, 91–108.
40. Whiteneck, G.G., Cuthbert, J.P., Corrigan, J.D., and Bogner, J.A. (2016). Prevalence of Self-Reported Lifetime History of Traumatic Brain Injury and Associated Disability: A Statewide Population-Based Survey. *J. Head Trauma Rehabil.* 31, E55–E62.
41. Pearson, W.S., Sugerman, D.E., McGuire, L.C., and Coronado, V.G. (2012). Emergency department visits for traumatic brain injury in older adults in the United States: 2006–08. *West J. Emerg. Med.* 13, 289–293.
42. C.D.C. (2016). Traumatic Brain Injury & Concussion: TBI Data and Statistics. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control: Atlanta, GA. Available at: <https://www.cdc.gov/traumaticbraininjury/data/index.html> (last accessed January 30, 2017).
43. Nwaiwu, O., Phillips, C., and Ohsfeldt, R. (2016). Trends in Hospitalization of Older Adults with Traumatic Brain Injury. *J. Am. Geriatr. Soc.* 64, e99–e100.
44. Fletcher, A.E., Khalid, S., and Mallonee, S. (2007). The epidemiology of severe traumatic brain injury among persons 65 years of age and older in Oklahoma, 1992–2003. *Brain Inj.* 21, 691–699.
45. Haring, R.S., Narang, K., Canner, J.K., Asemota, A.O., George, B.P., Selvarajah, S., Haider, A.H., and Schneider, E.B. (2015). Traumatic brain injury in the elderly: morbidity and mortality trends and risk factors. *J. Surg. Res.* 195, 1–9.
46. Pérez, K., Novoa, A.M., Santamariña-Rubio, E., Narvaez, Y., Arzufat, V., Borrell, C., Cabeza, E., Cirera, E., Ferrando, J., García-Altés, A., Gonzalez-Luque, J.C., Lizarbe, V., Martín-Cantera, C., Seguí-Gómez, M., and Suelves, J.M.; Working Group for Study of Injuries of Spanish Society of Epidemiology (2012). Incidence trends of traumatic spinal cord injury and traumatic brain injury in Spain, 2000–2009. *Accid. Anal. Prev.* 46, 37–44.
47. Hawley, C., Sakr, M., Scapinello, S., Salvo, J., and Wrenn, P. (2017). Traumatic brain injuries in older adults—6 years of data for one UK trauma centre: retrospective analysis of prospectively collected data. *Emerg. Med. J.* 34, 509–516.
48. Hamill, V., Barry, S.J.E., McConnachie, A., McMillan, T.M., and Teasdale, G.M. (2015). Mortality from head injury over four decades in Scotland. *J. Neurotrauma* 32, 689–703.
49. Scholten, A.C., Haagsma, J.A., Panneman, M.J., van Beeck, E.F., and Polinder, S. (2014). Traumatic brain injury in the Netherlands: incidence, costs and disability-adjusted life years. *PLoS One* 9, e110905.
50. Brazinova, A., Mauritz, W., Majdan, M., Rehorekova, V., and Leitgeb, J. (2015). Fatal traumatic brain injury in older adults in Austria 1980–2012: an analysis of 33 years. *Age Ageing* 44, 502–506.
51. Korhonen, N., Niemi, S., Parkkari, J., Sievanen, H., and Kannus, P. (2013). Incidence of fall-related traumatic brain injuries among older Finnish adults between 1970 and 2011. *JAMA* 309, 1891–1892.
52. Fu, T.S., Jing, R., McFaull, S.R., and Cusimano, M.D. (2015). Recent trends in hospitalization and in-hospital mortality associated with traumatic brain injury in Canada: a nationwide, population-based study. *J. Trauma Acute Care Surg.* 79, 449–455.
53. de Guise, E., LeBlanc, J., Dagher, J., Tinawi, S., Lamoureux, J., Marcoux, J., Maleki, M., and Feyz, M. (2014). Trends in Hospitalization Associated with TBI in an Urban Level 1 Trauma Centre. *Can. J. Neurol. Sci.* 41, 466–475.
54. Chan, V., Zagorski, B., Parsons, D., and Colantonio, A. (2013). Older adults with acquired brain injury: a population based study. *BMC Geriatr.* 13, 97.
55. Setnik, L., and Bazarian, J.J. (2007). The characteristics of patients who do not seek medical treatment for traumatic brain injury. *Brain Inj.* 21, 1–9.
56. Albrecht, J.S., Hirshon, J.M., McCunn, M., Bechtold, K.T., Rao, V., Simoni-Wastila, L., and Smith, G.S. (2016). Increased Rates of Mild Traumatic Brain Injury Among Older Adults in US Emergency Departments, 2009–2010. *J. Head Trauma Rehabil.* 31, E1–E7.
57. Centers for Disease Control and Prevention (CDC). (2003). Nonfatal fall-related traumatic brain injury among older adults—California, 1996–1999. *MMWR Morb. Mortal. Wkly. Rep.* 52, 276–278.
58. Herou, E., Romner, B., and Tomasevic, G. (2015). Acute traumatic brain injury: mortality in the elderly. *World Neurosurg.* 83, 996–1001.

59. Alberico, A.M., Ward, J.D., Choi, S.C., Marmarou, A., and Young, H.F. (1987). Outcome after severe head injury. Relationship to mass lesions, diffuse injury, and ICP course in pediatric and adult patients. *J. Neurosurg.* 67, 648–656.
60. Xiang, H., Kelleher, K., Shields, B.J., Brown, K.J., and Smith, G.A. (2005). Skiing- and snowboarding-related injuries treated in U.S. emergency departments, 2002. *J. Trauma* 58, 112–118.
61. Scheiman, S., Moghaddas, H.S., Bjornstig, U., Bylund, P.O., and Saveman, B.I. (2010). Bicycle injury events among older adults in Northern Sweden: a 10-year population based study. *Accid. Anal. Prev.* 42, 758–763.
62. Ortman, J.M., Velkoff, V.A., and Hogan, H. (2014). *An Aging Nation: The Older Population in the United States, Population Estimates and Projections.* Current Population Reports, United States Census Bureau: Washington, DC.
63. Mackenzie, E.J., Rivara, F.P., Jurkovich, G.J., Nathens, A.B., Frey, K.P., Egleston, B.L., Salkever, D.S., Weir, S., and Scharfstein, D.O. (2007). The National Study on Costs and Outcomes of Trauma. *J. Trauma* 63, S54–S67; discussion, S81–S56.
64. Thompson, H.J., Weir, S., Rivara, F.P., Wang, J., Sullivan, S.D., Salkever, D., and MacKenzie, E.J. (2012). Utilization and costs of health care after geriatric traumatic brain injury. *J. Neurotrauma* 29, 1864–1871.
65. Kumar, R.G., Juengst, S.B., Wang, Z., Dams-O'Connor, K., Dikmen, S.S., O'Neil-Pirozzi, T.M., Dahdah, M.N., Hammond, F.M., Felix, E.R., Arenth, P.M., and Wagner, A.K. (2018). Epidemiology of Comorbid Conditions Among Adults 50 Years and Older With Traumatic Brain Injury. *J. Head Trauma Rehabil.* 33, 15–24.
66. Ho, C.H., Hsieh, K.Y., Liang, F.W., Li, C.J., Wang, J.J., Chio, C.C., Chang, C.H., and Kuo, J.R. (2014). Pre-existing hyperlipidaemia increased the risk of new-onset anxiety disorders after traumatic brain injury: a 14-year population-based study. *BMJ Open* 4, e005269.
67. Leibson, C.L., Brown, A.W., Hall Long, K., Ransom, J.E., Mandrekar, J., Osler, T.M., and Malec, J.F. (2012). Medical care costs associated with traumatic brain injury over the full spectrum of disease: a controlled population-based study. *J. Neurotrauma* 29, 2038–2049.
68. McMillan, T.M., Weir, C.J., and Wainman-Lefley, J. (2014). Mortality and morbidity 15 years after hospital admission with mild head injury: a prospective case-controlled population study. *J. Neurol. Neurosurg. Psychiatry* 85, 1214–1220.
69. Gardner, R.C., Peltz, C.B., Kenney, K., Covinsky, K.E., Diaz-Arrastia, R., and Yaffe, K. (2017). Remote Traumatic Brain Injury Is Associated with Motor Dysfunction in Older Military Veterans. *J. Gerontol. A Biol. Sci. Med. Sci.* 72, 1233–1238.
70. Tinetti, M.E., Doucette, J., Claus, E., and Marottoli, R. (1995). Risk factors for serious injury during falls by older persons in the community. *J. Am. Geriatr. Soc.* 43, 1214–1221.
71. Tinetti, M.E., Speechley, M., and Ginter, S.F. (1988). Risk factors for falls among elderly persons living in the community. *N. Engl. J. Med.* 319, 1701–1707.
72. Shumway-Cook, A., Ciol, M.A., Hoffman, J., Dudgeon, B.J., Yorkston, K., and Chan, L. (2009). Falls in the Medicare population: incidence, associated factors, and impact on health care. *Phys. Ther.* 89, 324–332.
73. Corrigan, J.D., Bogner, J., Mellick, D., Bushnik, T., Dams-O'Connor, K., Hammond, F.M., Hart, T., and Kolakowsky-Hayner, S. (2013). Prior history of traumatic brain injury among persons in the Traumatic Brain Injury Model Systems National Database. *Arch. Phys. Med. Rehabil.* 94, 1940–1950.
74. Dams-O'Connor, K., Spielman, L., Singh, A., Gordon, W.A., Lingsma, H.F., Maas, A.I., Manley, G.T., Mukherjee, P., Okonkwo, D.O., Puccio, A.M., Schnyer, D.M., Valadka, A.B., Yue, J.K., and Yuh, E.L. (2013). The impact of previous traumatic brain injury on health and functioning: a TRACK-TBI study. *J. Neurotrauma* 30, 2014–2020.
75. Lew, H.L., Lee, E., Date, E.S., and Zeiner, H. (2002). Influence of medical comorbidities and complications on FIM change and length of stay during inpatient rehabilitation. *Am. J. Phys. Med. Rehabil.* 81, 830–837.
76. Lecours, A., Sirois, M.J., Ouellet, M.C., Boivin, K., and Simard, J.F. (2012). Long-term functional outcome of older adults after a traumatic brain injury. *J. Head Trauma Rehabil.* 27, 379–390.
77. Selassie, A.W., McCarthy, M.L., Ferguson, P.L., Tian, J., and Langlois, J.A. (2005). Risk of posthospitalization mortality among persons with traumatic brain injury, South Carolina 1999–2001. *J. Head Trauma Rehabil.* 20, 257–269.
78. Hirshson, C.I., Gordon, W.A., Singh, A., Ambrose, A., Spielman, L., Dams-O'Connor, K., Cantor, J., and Dijkers, M. (2013). Mortality of elderly individuals with TBI in the first 5 years following injury. *NeuroRehabilitation* 32, 225–232.
79. Dutton, R.P., Stansbury, L.G., Leone, S., Kramer, E., Hess, J.R., and Scalea, T.M. (2010). Trauma mortality in mature trauma systems: are we doing better? An analysis of trauma mortality patterns, 1997–2008. *J. Trauma* 69, 620–626.
80. Kahl, J.E., Calvo, R.Y., Sise, M.J., Sise, C.B., Thorndike, J.F., and Shackford, S.R. (2013). The changing nature of death on the trauma service. *J. Trauma Acute Care Surg.* 75, 195–201.
81. Kristman, V.L., Brison, R.J., Bedard, M., Reguly, P., and Chisholm, S. (2016). Prognostic markers for poor recovery after mild traumatic brain injury in older adults: a pilot cohort study. *J. Head Trauma Rehabil.* 31, E33–E43.
82. Peterson, M.G., Cornell, C.N., Paget, S.A., and Allegrante, J.P. (2008). Five-year survival in a cohort of hip fracture patients: the predictive role of pre-fracture health status. *HSS J.* 4, 43–47.
83. Covinsky, K.E., Palmer, R.M., Counsell, S.R., Pine, Z.M., Walter, L.C., and Chren, M.M. (2000). Functional status before hospitalization in acutely ill older adults: validity and clinical importance of retrospective reports. *J. Am. Geriatr. Soc.* 48, 164–169.
84. Fortinsky, R.H., Covinsky, K.E., Palmer, R.M., and Landefeld, C.S. (1999). Effects of functional status changes before and during hospitalization on nursing home admission of older adults. *J. Gerontol. A Biol. Sci. Med. Sci.* 54, M521–M526.
85. Covinsky, K.E., Justice, A.C., Rosenthal, G.E., Palmer, R.M., and Landefeld, C.S. (1997). Measuring prognosis and case mix in hospitalized elders. The importance of functional status. *J. Gen. Intern. Med.* 12, 203–208.
86. Evans, D.C., Cook, C.H., Christy, J.M., Murphy, C.V., Gerlach, A.T., Eiferman, D., Lindsey, D.E., Whitmill, M.L., Papadimos, T.J., Beery, P.R. II, Steinberg, S.M., and Stawicki, S.P. (2012). Comorbidity-polypharmacy scoring facilitates outcome prediction in older trauma patients. *J. Am. Geriatr. Soc.* 60, 1465–1470.
87. Joseph, B., Pandit, V., Zangbar, B., Kulvatunyou, N., Hashmi, A., Green, D.J., O'Keefe, T., Tang, A., Vercruyse, G., Fain, M.J., Friese, R.S., and Rhee, P. (2014). Superiority of frailty over age in predicting outcomes among geriatric trauma patients: a prospective analysis. *JAMA Surg.* 149, 766–772.
88. Crossley, M., Shiel, A., Wilson, B., Coleman, M.R., Gelling, L., Fryer, T., Boniface, S., and Pickard, J. (2005). Monitoring emergence from coma following severe brain injury in an octogenarian using behavioural indicators, electrophysiological measures and metabolic studies: a demonstration of the potential for good recovery in older adults. *Brain Inj.* 19, 729–737.
89. Rapoport, M.J. and Feinstein, A. (2000). Outcome following traumatic brain injury in the elderly: a critical review. *Brain Inj.* 14, 749–761.
90. Goldstein, F.C., Levin, H.S., Goldman, W.P., Kalechstein, A.D., Clark, A.N., and Kenehan-Altonen, T. (1999). Cognitive and behavioral sequelae of closed head injury in older adults according to their significant others. *J. Neuropsychiatry Clin. Neurosci.* 11, 38–44.
91. Livingston, D.H., Lavery, R.F., Mosenthal, A.C., Knudson, M.M., Lee, S., Morabito, D., Manley, G.T., Nathens, A., Jurkovich, G., Hoyt, D.B., and Coimbra, R. (2005). Recovery at one year following isolated traumatic brain injury: a Western Trauma Association prospective multicenter trial. *J. Trauma* 59, 1298–1304; discussion, 1304.
92. Raj, R., Mikkonen, E.D., Kivisaari, R., Skrifvars, M.B., Korja, M., and Siironen, J. (2016). Mortality in elderly patients operated for an acute subdural hematoma: a surgical case series. *World Neurosurg.* 88, 592–597.
93. Harvey, L.A., Mitchell, R., Brodaty, H., Draper, B., and Close, J.C. (2017). Comparison of fall-related traumatic brain injury in residential aged care and community-dwelling older people: a population-based study. *Australas. J. Ageing* 36, 144–150.
94. Bloch, F. (2016). Is the Glasgow Coma Scale appropriate for the evaluation of elderly patients in long-term care units? *J. Eval. Clin. Pract.* 22, 455–456.

95. Papa, L., Mendes, M.E., and Braga, C.F. (2012). Mild traumatic brain injury among the geriatric population. *Curr. Transl. Geriatr. Gerontol. Rep.* 1, 135–142.
96. Kehoe, A., Rennie, S. and Smith, J.E. (2015). Glasgow Coma Scale is unreliable for the prediction of severe head injury in elderly trauma patients. *Emerg. Med. J.* 32, 613–615.
97. Rothweiler, B., Temkin, N.R., and Dikmen, S.S. (1998). Aging effect on psychosocial outcome in traumatic brain injury. *Arch. Phys. Med. Rehabil.* 79, 881–887.
98. Mitra, B., Cameron, P.A., Gabbe, B.J., Rosenfeld, J.V., and Kavar, B. (2008). Management and hospital outcome of the severely head injured elderly patient. *ANZ J. Surg.* 78, 588–592.
99. Brazinova, A., Mauritz, W., Leitgeb, J., Wilbacher, I., Majdan, M., Janciak, I., and Rusnak, M. (2010). Outcomes of patients with severe traumatic brain injury who have Glasgow Coma Scale scores of 3 or 4 and are over 65 years old. *J. Neurotrauma* 27, 1549–1555.
100. Stocchetti, N., Paternò, R., Citerio, G., Beretta, L., and Colombo, A. (2012). Traumatic brain injury in an aging population. *J. Neurotrauma* 29, 1119–1125.
101. Styrke, J., Staltnacke, B.M., Sojka, P., and Bjornstig, U. (2007). Traumatic brain injuries in a well-defined population: epidemiological aspects and severity. *J. Neurotrauma* 24, 1425–1436.
102. Haydel, M.J., Preston, C.A., Mills, T.J., Luber, S., Blaudeau, E., and DeBlieux, P.M. (2000). Indications for computed tomography in patients with minor head injury. *N. Engl. J. Med.* 343, 100–105.
103. Stiell, I.G., Wells, G.A., Vandemheen, K., Clement, C., Lesiuk, H., Laupacis, A., McKnight, R.D., Verbeek, R., Brison, R., Cass, D., Eisenhauer, M.E., Greenberg, G., and Worthington, J. (2001). The Canadian CT Head Rule for patients with minor head injury. *Lancet* 357, 1391–1396.
104. Altman, J., Neustadtl, A., Milzman, D., Rao, S., Dubin, J., and Milzman, D. (2015). Lack of utility of head ct in concussive injury in non-geriatric ED patients. *Acad. Emerg. Med.* 22, S255.
105. Yuh, E.L., Mukherjee, P., Lingsma, H.F., Yue, J.K., Ferguson, A.R., Gordon, W.A., Valadka, A.B., Schnyer, R.M., Okonkwo, D.O., Maas, A.I., and Manley, G.T.; TRACK-TBI Investigators. (2013). Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury. *Ann. Neurol.* 73, 224–235.
106. Schonberger, M., Ponsford, J., Reutens, D., Beare, R., and O'Sullivan, R. (2009). The Relationship between age, injury severity, and MRI findings after traumatic brain injury. *J. Neurotrauma* 26, 2157–2167.
107. Chen, D.Y., Hsu, H.L., Kuo, Y.S., Wu, C.W., Chiu, W.T., Yan, F.X., Wang, W.S., Chen, C.J., and Tseng, Y.C. (2016). Effect of Age on Working Memory Performance and Cerebral Activation after Mild Traumatic Brain Injury: A Functional MR Imaging Study. *Radiology* 278, 854–862.
108. Yang, S.T., Hsiao, I.T., Hsieh, C.J., Chiang, Y.H., Yen, T.C., Chiu, W.T., Lin, K.J., and Hu, C.J. (2015). Accumulation of amyloid in cognitive impairment after mild traumatic brain injury. *J. Neurol. Sci.* 349, 99–104.
109. Hong, Y.T., Veenith, T., Dewar, D., Outtrim, J.G., Mani, V., Williams, C., Pimlott, S., Hutchinson, P.J., Tavares, A., Canales, R., Mathis, C.A., Klunk, W.E., Aigbirhio, F.I., Coles, J.P., Baron, J.C., Pickard, J.D., Fryer, T.D., Stewart, W., and Menon, D.K. (2014). Amyloid imaging with carbon 11-labeled Pittsburgh compound B for traumatic brain injury. *JAMA Neurol.* 71, 23–31.
110. Braak, H., and Braak, E. (1997). Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol. Aging* 18, 351–357.
111. Rice, D., Wang, K.K.W., and Robicsek, S. (2012). Biomarkers of traumatic brain injury in the geriatric population. *Curr Transl Geriatr Gerontol Rep.* 1, 129–134.
112. Thompson, H., Rivara, F., Becker, K., Temkin, N., and Maier, R. (2013). Considerations in the design and implementation of translational research using the traumatic brain injury common data elements. *J. Neurotrauma* 30, A79–A80.
113. Calcagnile, O., Holmen, A., Chew, M., and Unden, J. (2013). S100B levels are affected by older age but not by alcohol intoxication following mild traumatic brain injury. *Scand J Trauma Resusc Emerg Med.* 21, 52.
114. Mellergard, P., Sjogren, F., and Hillman, J. (2012). The cerebral extracellular release of glycerol, glutamate, and FGF2 is increased in older patients following severe traumatic brain injury. *J. Neurotrauma* 29, 112–118.
115. Mehan, N.D., and Strauss, K.I. (2012). Combined age- and trauma-related proteomic changes in rat neocortex: a basis for brain vulnerability. *Neurobiol. Aging* 33, 1857–1873.
116. Sandhir, R., Onyszchuk, G., and Berman, N.E.J. (2008). Exacerbated glial response in the aged mouse hippocampus following controlled cortical impact injury. *Exp. Neurol.* 213, 372–380.
117. Morganti, J.M., Riparip, L.K., Chou, A., Liu, S., Gupta, N., and Rosi, S. (2016). Age exacerbates the CCR2/5-mediated neuroinflammatory response to traumatic brain injury. *J. Neuroinflammation* 13, 80.
118. Calcagnile, O., Anell, A., and Unden, J. (2016). The addition of S100B to guidelines for management of mild head injury is potentially cost saving. *BMC Neurol.* 16, 200.
119. Krabbe, K.S., Pedersen, M., and Bruunsgaard, H. (2004). Inflammatory mediators in the elderly. *Exp. Gerontol.* 39, 687–699.
120. Bruunsgaard, H., and Pedersen, B.K. (2003). Age-related inflammatory cytokines and disease. *Immunol. Allergy Clin. North Am.* 23, 15–39.
121. Faul, M., Xu, L., and Sasser, S.M. (2016). Hospitalized traumatic brain injury: low trauma center utilization and high interfacility transfers among older adults. *Prehosp. Emerg. Care* 20, 594–600.
122. Salottolo, K., Levy, A.S., Slone, D.S., Mains, C.W., and Bar-Or, D. (2014). The effect of age on Glasgow Coma Scale score in patients with traumatic brain injury. *JAMA Surg.* 149, 727–734.
123. Werman, H.A., Erskine, T., Caterino, J., Riebe, J.F., and Valasek, T. (2011). Development of statewide geriatric patients trauma triage criteria. *Prehosp. Disaster Med.* 26, 170–179.
124. Wasserman, E.B., Shah, M.N., Jones, C.M., Cushman, J.T., Caterino, J.M., Bazarian, J.J., Gillespie, S.M., Cheng, J.D., and Dozier, A. (2015). Identification of a neurologic scale that optimizes EMS detection of older adult traumatic brain injury patients who require transport to a trauma center. *Prehosp. Emerg. Care* 19, 202–212.
125. Caterino, J.M., Raubenolt, A., and Cudnik, M.T. (2011). Modification of Glasgow Coma Scale criteria for injured elders. *Acad. Emerg. Med.* 18, 1014–1021.
126. Miller, E.C., Holmes, J.F., and Derlet, R.W. (1997). Utilizing clinical factors to reduce head CT scan ordering for minor head trauma patients. *J. Emerg. Med.* 15, 453–457.
127. Mower, W.R., Hoffman, J.R., Herbert, M., Wolfson, A.B., Pollack, C.V., Jr., and Zucker, M.I.; NEXUS II Investigators. (2005). Developing a decision instrument to guide computed tomographic imaging of blunt head injury patients. *J. Trauma* 59, 954–959.
128. Wolf, H., Machold, W., Frantal, S., Kecht, M., Pajenda, G., Leitgeb, J., Widhalm, H., Hajdu, S., and Sarahrudi, K. (2014). Risk factors indicating the need for cranial CT scans in elderly patients with head trauma: an Austrian trial and comparison with the Canadian CT Head Rule. *J. Neurosurg.* 120, 447–452.
129. Jagoda, A.S., Bazarian, J.J., Bruns, J.J., Jr., Cantrill, S.V., Gean, A.D., Howard, P.K., Ghajar, J., Riggio, S., Wright, D.W., Wears, R.L., Bakshy, A., Burgess, P., Wald, M.M., and Whitson, R.R.; American College of Emergency Physicians; Centers for Disease Control and Prevention. (2008). Clinical policy: neuroimaging and decisionmaking in adult mild traumatic brain injury in the acute setting. *Ann. Emerg. Med.* 52, 714–748.
130. Gore, A., Mau, C.Y., Prestigiacomo, C.J., and Sifri, Z.C. (2015). Mild traumatic brain injury in elderly patients: is routine ICU admission necessary? *J. Am. Coll. Surg.* 221, S82–S83.
131. Howard, B.M., Rindler, R.S., Holland, C.M., Pradilla, G., and Ahmad, F.U. (2017). Management and Outcomes of Isolated Tentorial and Parafalcine “Smear” Subdural Hematomas at a Level-I Trauma Center: Necessity of High Acuity Care. *J. Neurotrauma* 34, 128–136.
132. De Bonis, P., Pompucci, A., Mangiola, A., Paternoster, G., Festa, R., Nucci, C.G., Maviglia, R., Antonelli, M., and Anile, C. (2011). Decompressive craniectomy for elderly patients with traumatic brain injury: it's probably not worth the while. *J. Neurotrauma* 28, 2043–2048.
133. Giovine, Z., Campbell, D., Whitmill, M., Markert, R., and Saxe, J. (2014). Do all elderly patients with mild traumatic brain injury require admission? *Brain Inj.* 28, 769–770.
134. You, W., Feng, J., Tang, Q., Cao, J., Wang, L., Lei, J., Mao, Q., Gao, G., and Jiang, J. (2016). Intraventricular intracranial pressure monitoring improves the outcome of older adults with severe traumatic brain injury: an observational, prospective study. *BMC Anesthesiol.* 16, 35.
135. Dang, Q., Simon, J., Catino, J., Puente, I., Habib, F., Zucker, L., and Bukur, M. (2015). More fateful than fruitful? Intracranial pressure

- monitoring in elderly patients with traumatic brain injury is associated with worse outcomes. *J. Surg. Res.* 198, 482–488.
136. Kinoshita, T., Yoshiya, K., Fujimoto, Y., Kajikawa, R., Kiguchi, T., Hara, M., Wakayama, A. and Yoshimine, T. (2016). Decompressive craniectomy in conjunction with evacuation of intracranial hemorrhagic lesions is associated with worse outcomes in elderly patients with traumatic brain injury: a propensity score analysis. *World Neurosurg.* 89, 187–192.
  137. Czosnyka, M., Balestreri, M., Steiner, L., Smielewski, P., Hutchinson, P.J., Matta, B., and Pickard, J.D. (2005). Age, intracranial pressure, autoregulation, and outcome after brain trauma. *J. Neurosurg.* 102, 450–454.
  138. Wan, X., Liu, S., Wang, S., Zhang, S., Yang, H., Ou, Y., Zhao, M., James, L., Shu, K., Chen, J., and Lei, T. (2016). Elderly patients with severe traumatic brain injury could benefit from surgical treatment. *World Neurosurg.* 89, 147–152.
  139. Peck, K.A., Calvo, R.Y., Schechter, M.S., Sise, C.B., Kahl, J.E., Shackford, M.C., Shackford, S.R., Sise, M.J., and Blaskiewicz, D.J. (2014). The impact of preinjury anticoagulants and prescription antiplatelet agents on outcomes in older patients with traumatic brain injury. *J. Trauma Acute Care Surg.* 76, 431–436.
  140. Nishijima, D.K., Shahlaie, K., Sarkar, K., Rudisill, N., and Holmes, J.F. (2013). Risk of unfavorable long-term outcome in older adults with traumatic intracranial hemorrhage and anticoagulant or antiplatelet use. *Am. J. Emerg. Med.* 31, 1244–1247.
  141. Bauer, J., Harrison, G., Grandhi, R., Voronovich, Z., Puccio, A., and Okonkwo, D.O. (2012). Pre-morbid and hospital course factors affecting intracranial hemorrhage expansion and mortality in the elderly post traumatic brain injury. *J. Neurotrauma* 29, A44–A45.
  142. Pieracci, F.M., Eachempati, S.R., Shou, J., Hydo, L.J., and Barie, P.S. (2007). Degree of anticoagulation, but not warfarin use itself, predicts adverse outcomes after traumatic brain injury in elderly trauma patients. *J. Trauma* 63, 525–530.
  143. Grandhi, R., Harrison, G., Voronovich, Z., Bauer, J., Chen, S.H., Nicholas, D., Alarcon, L.H., and Okonkwo, D.O. (2015). Preinjury warfarin, but not antiplatelet medications, increases mortality in elderly traumatic brain injury patients. *J. Trauma Acute Care Surg.* 78, 614–621.
  144. Julien, J., Alsideiri, G., Marcoux, J., Hasen, M., Correa, J.A., Feyz, M., Maleki, M., and de Guise, E. (2017). Antithrombotic agents intake prior to injury does not affect outcome after a traumatic brain injury in hospitalized elderly patients. *J. Clin. Neurosci.* 38, 122–125.
  145. Panczykowski, D.M., and Okonkwo, D.O. (2011). Premorbid oral antithrombotic therapy and risk for reaccumulation, reoperation, and mortality in acute subdural hematomas. *J. Neurosurg.* 114, 47–52.
  146. Pieracci, F.M., Eachempati, S.R., Shou, J., Hydo, L.J., and Barie, P.S. (2007). Use of long-term anticoagulation is associated with traumatic intracranial hemorrhage and subsequent mortality in elderly patients hospitalized after falls: analysis of the New York State Administrative Database. *J. Trauma* 63, 519–524.
  147. Lucke-Wold, B.P., Turner, R.C., Josiah, D., Knotts, C., and Bhatia, S. (2016). Do age and anticoagulants affect the natural history of acute subdural hematomas? *Arch. Emerg. Med. Crit. Care* 1, 1010.
  148. Albrecht, J.S., Liu, X., Baumgarten, M., Langenberg, P., Rattinger, G.B., Smith, G.S., Gambert, S.R., Gottlieb, S.S., and Zuckerman, I.H. (2014). Benefits and risks of anticoagulation resumption following traumatic brain injury. *JAMA Intern. Med.* 174, 1244–1251.
  149. Mushkudiani, N.A., Engel, D.C., Steyerberg, E.W., Butcher, I., Lu, J., Marmarou, A., Sliker, F., McHugh, G.S., Murray, G.D., and Maas, A.I. (2007). Prognostic value of demographic characteristics in traumatic brain injury: results from the IMPACT study. *J. Neurotrauma* 24, 259–269.
  150. Valadka, A.B., and Sprunt, J.M. (2012). Craniotomy for acute subdural hematoma in the elderly: not as bad as you thought. *World Neurosurg.* 78, 231–232.
  151. MacKenzie, E.J., Rivara, F.P., Jurkovich, G.J., Nathens, A.B., Frey, K.P., Egleston, B.L., Salkever, D.S., and Scharfstein, D.O. (2006). A national evaluation of the effect of trauma-center care on mortality. *N. Engl. J. Med.* 354, 366–378.
  152. Mullins, R.J., Mann, N.C., Hedges, J.R., Worrall, W., Helfand, M., Zechin, A.D., and Jurkovich, G.J. (1998). Adequacy of hospital discharge status as a measure of outcome among injured patients. *JAMA* 279, 1727–1731.
  153. Merzo, A., Lenell, S., Nyholm, L., Enblad, P., and Lewen, A. (2016). Promising clinical outcome of elderly with TBI after modern neurointensive care. *Acta Neurochir.* 158, 125–133.
  154. McIntyre, A., Mehta, S., Janzen, S., Aubut, J., and Teasell, R.W. (2013). A meta-analysis of functional outcome among older adults with traumatic brain injury. *NeuroRehabilitation* 32, 409–414.
  155. Turgeon, A.F., Lauzier, F., Simard, J.F., Scales, D.C., Burns, K.E., Moore, L., Zygun, D.A., Bernard, F., Meade, M.O., Dung, T.C., Ratnapalan, M., Todd, S., Harlock, J., and Fergusson, D.A.; Canadian Critical Care Trials Group. (2011). Mortality associated with withdrawal of life-sustaining therapy for patients with severe traumatic brain injury: a Canadian multicentre cohort study. *CMAJ* 183, 1581–1588.
  156. Kirkman, M.A., Jenks, T., Bouamra, O., Edwards, A., Yates, D., and Wilson, M.H. (2013). Increased mortality associated with cerebral contusions following trauma in the elderly: bad patients or bad management? *J. Neurotrauma* 30, 1385–1390.
  157. Munro, P.T., Smith, R.D., and Parke, T.R. (2002). Effect of patients' age on management of acute intracranial haematoma: prospective national study. *BMJ* 325, 1001.
  158. McMillan, T., Wilson, L., Ponsford, J., Levin, H., Teasdale, G., and Bond, M. (2016). The Glasgow Outcome Scale—40 years of application and refinement. *Nat. Rev. Neurol.* 12, 477–485.
  159. National Institutes of Neurological Diseases and Stroke Common Data Elements: Traumatic Brain Injury [online]. National Institutes of Neurological Diseases and Stroke: Bethesda, MD.
  160. Haller, C.S., Delhumeau, C., De Pretto, M., Schumacher, R., Pielmaier, L., Rebetez, M.M., Haller, G., and Walder, B. (2017). Trajectory of disability and quality-of-life in non-geriatric and geriatric survivors after severe traumatic brain injury. *Brain Inj.* 1–10.
  161. Wilson, J.T., Pettigrew, L.E., and Teasdale, G.M. (1998). Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *J. Neurotrauma* 15, 573–585.
  162. Manley, G.T., and Maas, A.I. (2013). Traumatic brain injury: an international knowledge-based approach. *JAMA* 310, 473–474.
  163. (2015). TBI Endpoints Development (TED) Initiative—Expert Working Groups—Clinical Outcomes Assessment. University of California San Francisco, San Francisco, CA.
  164. Manley, G.T., MacDonald, C.L., Markowitz, A., Stephenson, D., Robbins, A., Gardner, R.C., Winkler, E.A., Bodien, Y., Taylor, S., Yue, J.K., Kannan, L., Kumar, A., McCrea, M., and Wang, K.K.W. (2017). The Traumatic Brain Injury Endpoints Development (TED) Initiative: Progress on a Public-Private Regulatory Collaboration to Accelerate Diagnosis and Treatment of Traumatic Brain Injury. *J. Neurotrauma*. Mar 31. doi: 10.1089/neu.2016.4729. [Epub ahead of print]
  165. Lin, Y.-N., Hwang, H.-F., Chen, Y.-J., Cheng, C.-H., Liang, W.-M., and Lin, M.-R. (2016). Suitability of the quality of life after brain injury instrument for older people with traumatic brain injury. *J. Neurotrauma* 33, 1363–1370.
  166. Kristman, V.L., Reguly, P., Brison, R., Bedard, M., and Chisholm, S. (2014). Comparison of outcome measures for studying mild traumatic brain injury prognosis in older adults. *Arch. Phys. Med. Rehabil.* 95, e69.
  167. Srivastava, A., Rapoport, M.J., Leach, L., Phillips, A., Shammi, P., and Feinstein, A. (2006). The utility of the Mini-Mental Status Exam in older adults with traumatic brain injury. *Brain Inj.* 20, 1377–1382.
  168. Ritchie, L., Wright-St Clair, V.A., Keogh, J., and Gray, M. (2014). Community integration after traumatic brain injury: a systematic review of the clinical implications of measurement and service provision for older adults. *Arch. Phys. Med. Rehabil.* 95, 163–174.
  169. Kinsella, G.J. (2010). Everyday memory for everyday tasks: prospective memory as an outcome measure following TBI in older adults. *Brain Impairment* 11, 37–41.
  170. Yokobori, S., Yamaguchi, M., Igarashi, Y., Hironaka, K., Onda, H., Kuwamoto, K., Araki, T., Fuse, A., and Yokota, H. (2016). Outcome and refractory factor of intensive treatment for geriatric traumatic brain injury: analysis of 1165 cases registered in the Japan Neurotrauma Data Bank. *World Neurosurg.* 86, 127–133.e1.
  171. Kristman, V.L., Brison, R.J., Bedard, M., Reguly, P., and Chisholm, S. (2016). Prognostic markers for poor recovery after mild traumatic brain injury in older adults: a pilot cohort study. *J. Head Trauma Rehabil.* 31, E33–E43.

172. Lenzi, J., Caporlingua, F., Caporlingua, A., Anichini, G., Nardone, A., Passacantilli, E., and Santoro, A. (2017). Relevancy of positive trends in mortality and functional recovery after surgical treatment of acute subdural hematomas. Our 10-year experience. *Br. J. Neurosurg.* 31, 78–83.
173. Lilley, E.J., Williams, K.J., Schneider, E.B., Hammouda, K., Salim, A., Haider, A.H., and Cooper, Z. (2016). Intensity of treatment, end-of-life care, and mortality for older patients with severe traumatic brain injury. *J. Trauma Acute Care Surg.* 80, 998–1004.
174. Dean, D., Martinez, M.S., and Newgard, C.D. (2015). Variability in early do not attempt resuscitation orders among patients with serious traumatic brain injury. *Acad. Emerg. Med.* 22, 54–60.
175. Flaada, J.T., Leibson, C.L., Mandrekar, J.N., Diehl, N., Perkins, P.K., Brown, A.W., and Malec, J.F. (2007). Relative risk of mortality after traumatic brain injury: a population-based study of the role of age and injury severity. *J. Neurotrauma* 24, 435–445.
176. Harrison-Felix, C., Kolakowsky-Hayner, S.A., Hammond, F.M., Wang, R., Englander, J., Dams-O'Connor, K., Kreider, S.E., Novack, T.A., and Diaz-Arrastia, R. (2012). Mortality after surviving traumatic brain injury: risks based on age groups. *J. Head Trauma Rehabil.* 27, E45–E56.
177. Annegers, J.F., and Coan, S.P. (2000). The risks of epilepsy after traumatic brain injury. *Seizure* 9, 453–457.
178. Annegers, J.F., Hauser, W.A., Coan, S.P., and Rocca, W.A. (1998). A population-based study of seizures after traumatic brain injuries. *N. Engl. J. Med.* 338, 20–24.
179. Asikainen, I., Kaste, M., and Sarna, S. (1999). Early and late post-traumatic seizures in traumatic brain injury rehabilitation patients: brain injury factors causing late seizures and influence of seizures on long-term outcome. *Epilepsia* 40, 584–589.
180. Vossel, K.A., Ranasinghe, K.G., Beagle, A.J., Mizuiri, D., Honma, S.M., Dowling, A.F., Darwish, S.M., Van Berlo, V., Barnes, D.E., Mantle, M., Karydas, A.M., Coppola, G., Roberson, E.D., Miller, B.L., Garcia, P.A., Kirscht, H.E., Mucke, L., and Nagarajan, S.S. (2016). Incidence and impact of subclinical epileptiform activity in Alzheimer's disease. *Ann. Neurol.* 80, 858–870.
181. Leppik, I.E., Bergey, G.K., Ramsay, R.E., Rowan, A.J., Gidal, B.E., Birnbaum, A.K., and Elliott, M.B. (2004). Advances in antiepileptic drug treatments. A rational basis for selecting drugs for older patients with epilepsy. *Geriatrics* 59, 14–18, 22–14.
182. Bergey, G.K. (2004). Initial treatment of epilepsy: special issues in treating the elderly. *Neurology* 63, S40–S48.
183. Albrecht, J.S., Liu, X.G., Smith, G.S., Baumgarten, M., Rattinger, G.B., Gambert, S.R., Langenberg, P., and Zuckerman, I.H. (2015). Stroke incidence following traumatic brain injury in older adults. *J. Head Trauma Rehabil.* 30, E62–E67.
184. Kowalski, R.G., Haarbauer-Krupa, J.K., Bell, J.M., Corrigan, J.D., Hammond, F.M., Torbey, M.T., Hofmann, M.C., Dams-O'Connor, K., Miller, A.C., and Whiteneck, G.G. (2017). Acute ischemic stroke after moderate to severe traumatic brain injury: incidence and impact on outcome. *Stroke* 48, 1802–1809.
185. Khokhar, B., Simoni-Wastila, L., and Albrecht, J.S. (2017). Risk of stroke among older Medicare antidepressant users with traumatic brain injury. *J. Head Trauma Rehabil.* 32, E42–E49.
186. Renoux, C., Vahey, S., Dell'Aniello, S., and Boivin, J.F. (2017). Association of selective serotonin reuptake inhibitors with the risk for spontaneous intracranial hemorrhage. *JAMA Neurol.* 74, 173–180.
187. Albrecht, J.S., Mullins, D.C., Smith, G.S., and Rao, V. (2017). Psychotropic medication use among Medicare beneficiaries following traumatic brain injury. *Am. J. Geriatr. Psychiatry* 25, 415–424.
188. Fleminger, S., Oliver, D.L., Lovestone, S., Rabe-Hesketh, S., and Giora, A. (2003). Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. *J. Neurol. Neurosurg. Psychiatry* 74, 857–862.
189. Mortimer, J.A., van Duijn, C.M., Chandra, V., Fratiglioni, L., Graves, A.B., Heyman, A., Jorm, A.F., Kokmen, E., Kondo, K., Rocca, W.A., Shalat, S.L., Soininen, H., and Hofman, A. (1991). Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. *Int. J. Epidemiol.* 20, Suppl. 2, S28–S35.
190. Perry, D.C., Sturm, V.E., Peterson, M.J., Pieper, C.F., Bullock, T., Boeve, B.F., Miller, B.L., Guskiewicz, K.M., Berger, M.S., Kramer, J.H., and Welsh-Bohmer, K.A. (2016). Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis. *J. Neurosurg.* 124, 511–526.
191. Jafari, S., Etmiman, M., Aminzadeh, F., and Samii, A. (2013). Head injury and risk of Parkinson disease: a systematic review and meta-analysis. *Mov. Disord.* 28, 1222–1229.
192. Luukinen, H., Viramo, P., Herala, M., Kervinen, K., Kesaniemi, Y.A., Savola, O., Winqvist, S., Jokelainen, J., and Hillbom, M. (2005). Fall-related brain injuries and the risk of dementia in elderly people: a population-based study. *Eur. J. Neurol.* 12, 86–92.
193. Barnes, D.E., Kaup, A., Kirby, K.A., Byers, A.L., Diaz-Arrastia, R., and Yaffe, K. (2014). Traumatic brain injury and risk of dementia in older veterans. *Neurology* 83, 312–319.
194. Rughjerg, K., Ritz, B., Korbo, L., Martinussen, N., and Olsen, J.H. (2008). Risk of Parkinson's disease after hospital contact for head injury: population based case-control study. *BMJ* 337, a2494.
195. Stern, R.A., Daneshvar, D.H., Baugh, C.M., Seichepine, D.R., Montenigro, P.H., Riley, D.O., Fritts, N.G., Stamm, J.M., Robbins, C.A., McHale, L., Simkin, I., Stein, T.D., Alvarez, V.E., Goldstein, L.E., Budson, A.E., Kowall, N.W., Nowinski, C.J., Cantu, R.C., and McKee, A.C. (2013). Clinical presentation of chronic traumatic encephalopathy. *Neurology* 81, 1122–1129.
196. McKee, A.C., Cantu, R.C., Nowinski, C.J., Hedley-Whyte, E.T., Gavett, B.E., Budson, A.E., Santini, V.E., Lee, H.S., Kubilus, C.A., and Stern, R.A. (2009). Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J. Neuropathol. Exp. Neurol.* 68, 709–735.
197. McKee, A.C., Cairns, N.J., Dickson, D.W., Folkerth, R.D., Keene, C.D., Litvan, I., Perl, D.P., Stein, T.D., Vonsattel, J.P., Stewart, W., Tripodis, Y., Crary, J.F., Bieniek, K.F., Dams-O'Connor, K., Alvarez, V.E., and Gordon, W.A.; TBI/CTE group. (2016). The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol.* 131, 75–86.
198. Koga, S., Dickson, D.W., and Bieniek, K.F. (2016). Chronic Traumatic Encephalopathy Pathology in Multiple System Atrophy. *J. Neuropathol. Exp. Neurol.* 75, 963–970.
199. Bieniek, K.F., Ross, O.A., Cormier, K.A., Walton, R.L., Soto-Ortolaza, A., Johnston, A.E., DeSaro, P., Boylan, K.B., Graff-Radford, N.R., Wszolek, Z.K., Rademakers, R., Boeve, B.F., McKee, A.C., and Dickson, D.W. (2015). Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank. *Acta Neuropathol.* 130, 877–889.
200. Yi, A., and Dams-O'Connor, K. (2013). Psychosocial functioning in older adults with traumatic brain injury. *NeuroRehabilitation* 32, 267–273.
201. Menzel, J.C. (2008). Depression in the elderly after traumatic brain injury: a systematic review. *Brain Inj.* 22, 375–380.
202. Albrecht, J.S., Kiptanui, Z., Tsang, Y., Khokhar, B., Liu, X.G., Simoni-Wastila, L., and Zuckerman, I.H. (2015). Depression among older adults after traumatic brain injury: a national analysis. *Am. J. Geriatr. Psychiatry* 23, 607–614.
203. Senathi-Raja, D., Ponsford, J., and Schonberger, M. (2010). The association of age and time postinjury with long-term emotional outcome following traumatic brain injury. *J. Head Trauma Rehabil.* 25, 330–338.
204. Rao, V. and Albrecht, J.S. (2016). Traumatic brain injury in the elderly and neuropsychiatric disturbances. *J. Neuropsychiatry Clin. Neurosci.* 28, e58.
205. Graham, J.E., Radice-Neumann, D.M., Reistetter, T.A., Hammond, F.M., Dijkers, M., and Granger, C.V. (2010). Influence of sex and age on inpatient rehabilitation outcomes among older adults with traumatic brain injury. *Arch. Phys. Med. Rehabil.* 91, 43–50.
206. Goldstein, F.C., Levin, H.S., Goldman, W.P., Clark, A.N., and Altonen, T.K. (2001). Cognitive and neurobehavioral functioning after mild versus moderate traumatic brain injury in older adults. *J. Int. Neuropsychol. Soc.* 7, 373–383.
207. Mathias, J.L., and Wheaton, P. (2015). Contribution of brain or biological reserve and cognitive or neural reserve to outcome after TBI: a meta-analysis (prior to 2015). *Neurosci. Biobehav. Rev.* 55, 573–593.
208. Kinsella, G.J., Olver, J., Ong, B., Gruen, R., and Hammersley, E. (2014). Mild traumatic brain injury in older adults: early cognitive outcome. *J. Int. Neuropsychol. Soc.* 20, 663–671.
209. MRC CRASH Trial Collaborators, Perel, P., Arango, M., Clayton, T., Edwards, P., Komolafe, E., Pocock, S., Roberts, I., Shakur, H., Steyerberg, E., and Yutthakasemsunt, S. (2008). Predicting outcome

- after traumatic brain injury: practical prognostic models based on large cohort of international patients. *BMJ* 336, 425–429.
210. Staples, J.A., Wang, J., Mills, B., Temkin, N., Zaros, M.C., Jurkovich, G.J., and Rivara, F.P. (2016). The Application of the CRASH-CT Prognostic Model for Older Adults With Traumatic Brain Injury: A Population-Based Observational Cohort Study. *J. Head Trauma Rehabil.* 31, E8–E14.
  211. Roe, C., Skandsen, T., Manskow, U., Ader, T., and Anke, A. (2015). Mortality and One-Year Functional Outcome in Elderly and Very Old Patients with Severe Traumatic Brain Injuries: Observed and Predicted. *Behav. Neurol.* 2015, 845491.
  212. Steyerberg, E.W., Mushkudiani, N., Perel, P., Butcher, I., Lu, J., McHugh, G.S., Murray, G.D., Marmarou, A., Roberts, I., Habbema, J.D., and Maas, A.I. (2008). Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Med* 5, e165; discussion, e165.
  213. Roozenbeek, B., Lingsma, H.F., Lecky, F.E., Lu, J., Weir, J., Butcher, I., McHugh, G.S., Murray, G.D., Perel, P., Maas, A.I., and Steyerberg, E.W.; International Mission on Prognosis Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT) Study Group; Corticosteroid Randomisation After Significant Head Injury (CRASH) Trial Collaborators; Trauma Audit and Research Network (TARN). (2012). Prediction of outcome after moderate and severe traumatic brain injury: external validation of the International Mission on Prognosis and Analysis of Clinical Trials (IMPACT) and Corticoid Randomisation After Significant Head Injury (CRASH) prognostic models. *Crit. Care Med.* 40, 1609–1617.
  214. Staples, J.A., Wang, J., Zaros, M.C., Jurkovich, G.J., and Rivara, F.P. (2016). The application of IMPACT prognostic models to elderly adults with traumatic brain injury: a population-based observational cohort study. *Brain Inj.* 30, 899–907.
  215. Uomoto, J.M. (2008). Older adults and neuropsychological rehabilitation following acquired brain injury. *NeuroRehabilitation* 23, 415–424.
  216. Dijkers, M., Brandstater, M., Horn, S., Ryser, D., and Barrett, R. (2013). Inpatient rehabilitation for traumatic brain injury: the influence of age on treatments and outcomes. *NeuroRehabilitation* 32, 233–252.
  217. Chang, P.F., Ostir, G.V., Kuo, Y.F., Granger, C.V. and Ottenbacher, K.J. (2008). Ethnic differences in discharge destination among older patients with traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, 231–236.
  218. Corrigan, J.D., Cuthbert, J.P., Whiteneck, G.G., Dijkers, M.P., Coronado, V., Heinemann, A.W., Harrison-Felix, C., and Graham, J.E. (2012). Representativeness of the Traumatic Brain Injury Model Systems National Database. *J. Head Trauma Rehabil.* 27, 391–403.
  219. Luoto, T.M., Tenovu, O., Kataja, A., Brander, A., Ohman, J. and Iverson, G.L. (2013). Who gets recruited in mild traumatic brain injury research? *J. Neurotrauma* 30, 11–16.
  220. Roozenbeek, B., Maas, A.I.R., Marmarou, A., Butcher, I., Lingsma, H.F., Lu, J., McHugh, G.S., Murray, G.D., and Steyerberg, E.W. (2009). The influence of enrollment criteria on recruitment and outcome distribution in traumatic brain injury studies: results from the IMPACT study. *J. Neurotrauma* 26, 1069–1075.
  221. Maas, A.I., Murray, G.D., Roozenbeek, B., Lingsma, H.F., Butcher, I., McHugh, G.S., Weir, J., Lu, J. and Steyerberg, E.W. (2013). Advancing care for traumatic brain injury: findings from the IMPACT studies and perspectives on future research. *Lancet Neurol.* 12, 1200–1210.
  222. Gaastra, B., Longworth, A., Matta, B., Snelson, C., Whitehouse, T., Murphy, N., and Veenith, T. (2016). The ageing population is neglected in research studies of traumatic brain injury. *Br. J. Neurosurg.* 30, 221–226.
  223. McCullagh, S., and Feinstein, A. (2003). Outcome after mild traumatic brain injury: an examination of recruitment bias. *J. Neurol. Neurosurg. Psychiatry* 74, 39–43.
  224. Trivedi, R.B., and Humphreys, K. (2015). Participant exclusion criteria in treatment research on neurological disorders: are unrepresentative study samples problematic? *Contemp. Clin. Trials* 44, 20–25.
  225. Renfro, M., Bainbridge, D.B., and Smith, M.L. (2016). Validation of Evidence-Based Fall Prevention Programs for Adults with Intellectual and/or Developmental Disorders: A Modified Otago Exercise Program. *Front. Public Health* 4, 261.
  226. Holmes, J.F., Palchak, M.J., MacFarlane, T., and Kuppermann, N. (2005). Performance of the pediatric glasgow coma scale in children with blunt head trauma. *Acad. Emerg. Med.* 12, 814–819.
  227. Borgianni, D.A., Mahajan, P., Hoyle, J.D., Jr., Powell, E.C., Nadel, F.M., Tunik, M.G., Foerster, A., Dong, L., Miskin, M., Dayan, P.S., Holmes, J.F., and Kuppermann, N.; Pediatric Emergency Care Applied Research Network (PECARN). (2016). Performance of the Pediatric Glasgow Coma Scale Score in the Evaluation of Children With Blunt Head Trauma. *Acad. Emerg. Med.* 23, 878–884.
  228. Beers, S.R., Wisniewski, S.R., Garcia-Filion, P., Tian, Y., Hahner, T., Berger, R.P., Bell, M.J., and Adelson, P.D. (2012). Validity of a pediatric version of the Glasgow Outcome Scale-Extended. *J. Neurotrauma* 29, 1126–1139.
  229. Røe, C., Skandsen, T., Manskow, U., Ader, T., and Anke, A. (2015). Mortality and one-year functional outcome in elderly and very old patients with severe traumatic brain injuries: observed and predicted. *Behav. Neurol.* 2015, 7.
  230. Okazaki, T., Hifumi, T., Kawakita, K., Nakashima, R., Matsumoto, A., Shishido, H., Ogawa, D., Okauchi, M., Shindo, A., Kawanishi, M., Tamiya, T., and Kuroda, Y. (2016). Association Between Comorbidities, Nutritional Status, and Anticlotting Drugs and Neurologic Outcomes in Geriatric Patients with Traumatic Brain Injury. *World Neurosurg.* 93, 336–340.
  231. Maiden, M.J., Gabbe, B.J., Rosenfeld, J.V., and Cameron, P.A. (2014). 12-Month outcomes in a cohort of older adults with severe traumatic brain injury admitted to an intensive care unit. *Am. J. Resp. Crit. Care Med.* 189, A2545.
  232. Utomo, W.K., Gabbe, B.J., Simpson, P.M., and Cameron, P.A. (2009). Predictors of in-hospital mortality and 6-month functional outcomes in older adults after moderate to severe traumatic brain injury. *Injury* 40, 973–977.
  233. Tokutomi, T., Miyagi, T., Ogawa, T., Ono, J., Kawamata, T., Sakamoto, T., Shigemori, M., and Nakamura, N. (2008). Age-associated increases in poor outcomes after traumatic brain injury: a report from the Japan Neurotrauma Data Bank. *J. Neurotrauma* 25, 1407–1414.
  234. Cheng, P.L., Lin, H.Y., Lee, Y.K., Hsu, C.Y., Lee, C.C., and Su, Y.C. (2014). Higher mortality rates among the elderly with mild traumatic brain injury: a nationwide cohort study. *Scand. J. Trauma Resusc. Emerg. Med.* 22, 7.
  235. Bhullar, I.S., Roberts, E.E., Brown, L. and Lipei, H. (2010). The effect of age on blunt traumatic brain-injured patients. *Am. Surg.* 76, 966–968.
  236. Susman, M., DiRusso, S.M., Sullivan, T., Risucci, D., Nealon, P., Cuff, S., Haider, A., and Benzil, D. (2002). Traumatic brain injury in the elderly: increased mortality and worse functional outcome at discharge despite lower injury severity. *J. Trauma* 53, 219–223; discussion, 223–224.

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