Evaluation of S100B in the diagnosis of suspected intracranial hemorrhage after minor head injury in patients who are receiving platelet aggregation inhibitors and in patients 65 years of age and older

*Heinrich Wolfgang Thaler, MD,¹ Jochen Schmidsfeld, MD,² Michael Pusch, MD,¹ Simon Pienaar, MD,¹ Jörg Wunderer, MD,¹ Paul Pittermann, MD,¹ Rosmarie Valenta, MD,³ Andreas Gleiss, PhD,⁴ Christian Fialka, MD,¹ and Mehdi Mousavi, MD²

¹Trauma Hospital Meidling; ²Department of Traumatology, Donauespital; and ³Department of Radiology, Kaiser-Franz-Josef-Spital, Vienna; and ⁴Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Austria

OBJECT Cranial CT (CCT) scans and hospital admission are increasingly performed to rule out intracranial hemorrhage in patients after minor head injury (MHI), particularly in older patients and in those receiving antiplatelet therapy. This leads to high radiation exposure and a growing financial burden. The aim of this study was to determine whether the astroglial-derived protein S100B that is released into blood can be used as a reliable negative predictive tool for intracranial bleeding in patients after MHI, when they are older than 65 years or being treated with antiplatelet drugs (low-dose aspirin, clopidogrel).

METHODS The authors conducted a prospective observational study in 2 trauma hospitals. A total of 782 patients with MHI (Glasgow Coma Scale Score 13–15) who were on medication with platelet aggregation inhibitors (PAIs) or were age 65 years and older, independent of antiplatelet therapy, were included. Clinical examination, bloodwork, observation, and CCT were performed in the traumatology emergency departments. When necessary, patients were admitted and observation took place on the ward; in these patients, CCT was performed during their hospital stay. Patients with severe trauma, focal neurological deficits, posttraumatic seizures, anticoagulant therapy, alcohol intoxication, coagulation disorder, blood sampling more than 3 hours after trauma, and unknown time of the trauma were excluded from the study. The median age of the patients was 83 years, and 69% were female. Sensitivity, specificity, and positive and negative predictive values of S100B with reference to CCT findings were calculated. The cutoff of S100B was set at 0.105 µg/L.

RESULTS Of the 782 patients, 50 (6.4%) had intracranial bleeding. One patient with positive results on CCT scan showed an S100B level below 0.105 µg/L. Of all patients, 33.1% were below the cutoff. S100B showed a sensitivity of 98.0% (CI 89.5%–99.7%), a negative predictive value of 99.6% (CI 97.9%–99.9%), a specificity of 35.3% (CI 31.9%–38.8%), and a positive predictive value of 9.4% (CI 7.2%–12.2%).

CONCLUSIONS Levels of S100B below 0.105 µg/L can accurately predict normal CCT findings after MHI in older patients and in those treated with PAIs. Combining conventional decision criteria with measurement of S100B can reduce the CCT scan and hospital admission rates by approximately 30%.

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KEY WORDS minor head injury; intracranial hemorrhage; S100B; platelet aggregation inhibitors; older patients; traumatic brain injury

ABBREVIATIONS CCT = cranial CT; ED = emergency department; GCS = Glasgow Coma Scale; IQR = interquartile range; MHI = minor head injury; NPV = negative predictive value; PAI = platelet aggregation inhibitor; PPV = positive predictive value.

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* Drs. Thaler and Schmidsfeld contributed equally to this work.

IN adults age 65 years and older, head injuries are frequently observed. As the aging population rapidly grows, the number of these mostly fall-related injuries increases at an even higher rate.^{8,30} Up to 90% of all treated head injuries are minor head injuries (MHIs), defined by a score of 13–15 on the Glasgow Coma Scale (GCS).^{29,36} They occur with an incidence of 60–300 per 100,000.¹¹ Intracranial bleeding is detected in approximately 7% of those patients, and they very rarely require neurosurgical intervention.^{1,9,13,16} To rule out intracranial hemorrhage, patients with MHI must undergo cranial CT (CCT) scans, and many of them are additionally hospitalized for observation. The decision criteria used in the management of MHI are not standardized and remain controversial.^{9,13,18,27,33}

In older patients and in patients on platelet aggregation inhibitors (PAIs), i.e., low-dose aspirin and clopidogrel, the common clinical practice is to perform a CCT scan, often combined with clinical observation, because these groups are assumed to have a higher rate of intracranial bleeding.^{4,6,15,28} In addition, they are also considered to suffer from delayed bleeding.^{20,28} Therefore, the rate of hospitalization more than doubles for patients age 65 years and older, compared with the general population with head injuries.³⁰ This is not only problematic with regard to the radiation exposure, but also represents an enormous financial burden.²⁴

In the last 20 years, evidence has shown that measurement of the protein S100B in serum has been useful in the management of MHI.^{2,12,14,17,22,32,34,38} S100B is a calcium-binding peptide that is mainly produced by astrocytes. Increased S100B concentrations after brain trauma are a consequence of the destruction of astrocytes combined with a temporary dysfunction of the blood-brain barrier.²¹ Together with the conventional clinical decision criteria, measurement of S100B levels can be used safely to exclude approximately 30% of adult patients from further diagnostic procedures like CCT if the blood sample is drawn within 3 hours after injury.^{2,14,17,34} This maximum time span is based on the short half-life of S100B (90 minutes).^{21,31} To date, the use of S100B as a screening tool to help exclude intracranial hemorrhage in the group of patients with MHI who are older than 65 years and in patients with MHI who are receiving PAI treatment has not been specifically examined. The aim of this study was to analyze whether S100B is a reliable negative predictive tool for intracranial bleeding after MHI in older age (older than 65 years) and in patients receiving PAIs. If so, the number of CCT scans and hospital admissions for observation could be significantly reduced.

Methods

Study Design

This prospective, observational study was conducted from May 2011 to October 2013 at 2 trauma centers in Vienna, Austria: the Trauma Center of Meidling and the Department of Traumatology at the Donauespital. The study protocol was approved by the ethics committees of the 2 participating centers. Informed consent was obtained for all patients in the emergency department (ED). For those

with GCS scores between 13 and 14, consent was obtained from the next of kin before admission. Informed consent for all patients was obtained within half an hour after arriving in the ED, and those who met the inclusion criteria were included in the study. Inclusion criteria were as follows: MHI (GCS Score 13–15) in patients on medication with PAI who were older than 18 years, and MHI in patients age 65 years and older independent of PAI intake. Patients with MHI and severe trauma (open fractures, large open wounds, clinical signs of basal skull fracture, polytrauma), focal neurological deficits, posttraumatic seizures, anticoagulant therapy (vitamin K antagonists, direct oral anticoagulants), alcohol intoxication, and with a history of a coagulation disorder were excluded. Additional exclusion criteria were blood sampling more than 3 hours after index event, unknown point in time of the trauma, and missing informed consent.

Patient-Related Data

The following patient-related data were collected: age, sex, GCS score, traumatological findings, circumstances of trauma, preexisting medical conditions, medication, laboratory findings (serum glucose, serum creatinine, C-reactive protein, hemoglobin, thrombocyte count, prothrombin time, and S100B), CCT findings, interval between trauma and blood draw, interval between trauma and CCT scan, and interval between trauma and hospital discharge. The reported dosing regimen for aspirin was 100 mg once daily, and for clopidogrel it was 75 mg once daily. The data were collected with a standardized protocol.

All patients were seen first in the traumatology ED by surgeons who determined the GCS score and performed a brief neurological examination. Patients with MHI who were receiving antiplatelet medication or who were older than 65 years were either admitted or observed for at least 6 hours. All patients underwent CCT. The decision whether a patient had to be admitted and the point in time at which CCT was performed depended on the clinical findings. When informed consent was given, a venous blood sample was drawn within 3 hours after injury and the S100B level was determined. The result of S100B analysis was not known to the attending physician. All clinical assessments were completed before the CCT scans were performed. The CCT findings and S100B results were included in the study database by different persons and at different points in time to avoid any influence. All patients were treated as they normally would have been, following the standard operating procedures of our institutions.

Cranial CT

For CCT diagnosis both study centers used multidetector computer tomography units (Siemens Somatom Open or Siemens Definition) with 3-mm slice thickness. Patients were classified into 2 groups: CCT negative (patients with MHI who had no signs of trauma-related intracranial bleeding) and CCT positive (patients with MHI who had at least 1 trauma-related intracranial hemorrhage: i.e., epidural, subdural, subarachnoidal, or intracerebral bleeding). Each CCT scan was interpreted by a consultant radiologist

who was blinded to the S100B level. The CCT results were spot-checked (25%) by an independent, experienced radiologist who was blinded to patient data.

Measurement of S100B

Blood was drawn from all patients and laboratory measurements were performed immediately. The time interval between the index event and the blood draw was limited to 3 hours, according to the manufacturer's recommendation; this time period is based on the half-life of about 90 minutes for the S100B molecule.^{21,31} All blood specimens were processed to serum. The serum S100B levels were determined by electrochemiluminescence immunoassay (Elecsys S100; Roche Diagnostics) on the Roche cobas e601 and cobas e411 instruments. The analytical range was 0.005–39 µg/L. The cutoff was set at 0.105 µg/L as stipulated by the manufacturer.

Statistical Analysis

The sample size for this study was chosen such that the Wilson 95% confidence interval for the negative predictive value (NPV) would be sufficiently narrow. For the cases of one or two false-negative results, the lower confidence limit should be above 97%. This could be reached by targeting at least 750 evaluable patients (based on an estimate of the rate of patients with S100B < 0.105 µg/L from the first 400 patients). Continuous variables are described by the median and interquartile range (IQR) due to their skewed distributions. Categorical variables are described by absolute frequencies and percentages and compared between groups by using chi-square tests. A trend of S100B across GCS categories was tested using a linear contrast with respect to log-transformed S100B. Sensitivity, specificity, positive predictive value (PPV), and NPV are reported with 95% Wilson confidence intervals. The area under the receiver operating characteristic curve is given with Wald confidence intervals. All calculations were done using SAS 9.4 software. Statistical tests were performed at a 2-sided 5% significance level.

Results

A total of 987 consecutive patients with MHI were considered for inclusion. In 192 patients the interval between trauma and blood sampling was more than 3 hours, and in 13 patients no CCT was performed; 782 patients therefore fulfilled all inclusion criteria. The demographic data and clinical characteristics are given in Table 1. The median age of the patients was 83 years (overall range 39–104 years, IQR 74–88 years), and 68.7% of the patients were female.

The median interval between event and blood drawing was 2:05 hours (IQR 1:30–2:30). The median interval between trauma and CCT was 15:40 hours (IQR 3:54–21:30). The median observation period was 31:37 hours (IQR 18:04–63:10). The predominant cause of trauma was a ground-level fall, followed by fall from a height. Traffic accidents were rare, and assaults were extremely rare. Most of our patients showed physical evidence of trauma above the clavicles. Nearly all patients had 1 or more pre-existing medical conditions, like hypertension, chronic

TABLE 1. Demographic and clinical characteristics in 782 patients with MHI

Characteristic	Value
Median age in yrs (IQR)	
Overall	83 (74–88)
Patients w/ PAI	83 (74–88)
Patients w/o PAI	82 (73–89)
Age & PAI status	
≥65 yrs w/ PAI	570 (72.9%)
≥65 yrs w/o PAI	151 (19.3%)
<65 yrs w/ PAI	61 (7.8%)
Sex	
Male	245 (31.3%)
Female	537 (68.7%)
Trauma history	
Fall on ground level	653 (83.5%)
Fall from height	58 (7.4%)
Traffic accident	27 (3.5%)
Other	28 (3.6%)
Unknown	16 (2.0%)
GCS score	
13	48 (6.1%)
14	147 (18.8%)
15	587 (75.1%)
PAIs	
Aspirin	526 (67.3%)
Clopidogrel	68 (8.7%)
Aspirin + clopidogrel	37 (4.7%)
None	151 (19.3%)

heart disease, diabetes mellitus, chronic obstructive pulmonary disease, osteoporosis, dementia, and Parkinson disease. Most of the patients were taking 2 or more drugs.

Of the 782 patients included, 732 (93.6%) proved to be CCT negative and 50 (6.4%) showed intracranial bleeding on CCT scans. Six hundred thirty-one patients (80.7%) were being treated with PAIs. The patient group without PAIs, who by definition of our inclusion criteria were 65 years and older, had a median age of 82 years (IQR 73–89). The patient group with PAIs had a median age of 83 years (IQR 74–88). Of the 631 patients on PAIs, 526 (83.3%) were taking low-dose aspirin, 68 (10.8%) were on clopidogrel, and 37 (5.9%) were taking both drugs. The respective number of intracranial hemorrhages was 32 (6.1%) in the aspirin group, 3 (4.4%) in the clopidogrel group, and 2 (5.4%) in the group on both drugs. Patients treated with PAIs had a lower rate of intracranial bleeding (5.9%) than those without PAIs (8.6%). This difference, however, is not statistically significant ($p = 0.215$) (Table 2).

Of the 782 patients, 587 (75.1%) had a GCS score of 15, 147 (18.8%) a GCS score of 14, and 48 (6.1%) were graded with a GCS score of 13. The number of CCT-positive patients was 23 (3.9%) in the GCS 15 group, 17 patients (11.6%) in the GCS 14 group, and 10 patients (20.8%) in

TABLE 2. Rates of intracranial bleeding in relation to PAI intake in 782 patients with MHI*

PAI Intake	No. of Patients	No. (%) of Intracranial Hemorrhages
Aspirin	526	32 (6.1%)
Clopidogrel	68	3 (4.4%)
Aspirin + clopidogrel	37	2 (5.4%)
All PAIs	631	37 (5.9%)
No PAI	151	13 (8.6%)

* There was no significant difference between patients with and without antiplatelet medication in regard to the rate of intracranial bleeding ($p = 0.215$).

the GCS 13 group (Table 3). The GCS score also correlated well with the S100B levels of these groups, showing higher values with worsening clinical symptoms ($p < 0.001$). There were 192 patients (24.6%) who presented with a history of loss of consciousness or posttraumatic amnesia.

In the CCT-positive group, 24 patients were diagnosed with subdural, 14 with intracerebral, and 12 with subarachnoid hematoma; no epidural hematoma was found (Table 4). Four of the 50 patients with hemorrhage presented with a skull fracture. No patient required a neurosurgical intervention. The median serum S100B concentration was 0.285 $\mu\text{g/L}$ (IQR 0.185–0.532) in this group. One of 50 patients with intracranial bleeding showed an S100B concentration below the cutoff value of 0.105 $\mu\text{g/L}$. This patient, a 95-year-old woman, had a nonfatal, small intracerebral hemorrhage near the cortex. Her GCS score was 15 and she had taken aspirin. The S100B serum concentration was 0.094 $\mu\text{g/L}$, the blood sample was taken 75 minutes after the trauma, and CCT scanning was performed 9 hours after the injury. In control CCT scans obtained 3 days after the event, the lesion had disappeared.

In the CCT-negative group, 35.3% showed S100B concentrations below the cutoff value of 0.105 $\mu\text{g/L}$; 64.7% were at or above the cutoff value. The median serum S100B concentration was 0.143 $\mu\text{g/L}$ (IQR 0.085–0.274) in this group.

The S100B results in the CCT-positive and CCT-negative groups are reported in Table 5. Calculation of sensitivity and specificity yielded the following results: 98.0% sensitivity (CI 89.5%–99.7%), NPV 99.6% (CI 97.9%–99.9%); 35.3% specificity (CI 31.9%–38.8%), PPV 9.4% (CI 7.2%–12.2%). Of all 782 patients, 259 (33.1%) showed an S100B value below the cutoff of 0.105 $\mu\text{g/L}$. The area under the receiver operating characteristic curve with respect to the radiological findings amounts to 0.73 (CI 0.67–0.79, $p < 0.001$).

Discussion

According to the recommendations from Haydel et al. (the so-called New Orleans Criteria), the “Canadian CT Head Rule,” and the “Scandinavian Guidelines for Initial Management of Minimal, Mild, and Moderate Head Injuries,” specific indicators exist to identify patients after MHI who should undergo CCT scanning.^{7,9,13,18,27,33} Two indicators in the patients’ history in particular—age great-

TABLE 3. GCS, S100B, and CCT findings in 782 patients with MHI

GCS Score*	CCT Negative	CCT Positive	Total	Median S100B Values (IQR)
13	38 (79.2%)	10 (20.8%)	48	0.284 $\mu\text{g/L}$ (0.130–0.652)
14	130 (88.4%)	17 (11.6%)	147	0.178 $\mu\text{g/L}$ (0.102–0.311)
15	564 (96.1%)	23 (3.9%)	587	0.139 $\mu\text{g/L}$ (0.085–0.267)
Total	732 (93.6%)	50 (6.4%)	782	0.150 $\mu\text{g/L}$ (0.088–0.291)

* GCS scores correlate well with S100B levels and with the rate of intracranial hemorrhage ($p < 0.001$).

er than 65 years and antiplatelet therapy—lead, regardless of the trauma-associated clinical aspects, to an overuse of CCT scans and observation.

The unacceptable increase of CCT and hospital admissions due to the use of these criteria was one of our reasons to perform this study. In this regard, the financial burden arising from the high CCT rates and the cost of hospital admission for observation, as well as the radiation-associated risks, are of major importance.^{3,24,25,37}

The economic impact of S100B as a screening test in the ED management of MHI in adult patients is discussed in detail by Ruan et al.²⁴ In that paper it was demonstrated that for S100B to be economical, more than 78% of patients with MHI must have undergone CCT. This is definitely the case in our specific patient group. Our study was performed in a central European urban region, in 2 large trauma hospitals, where the baseline rate of scanning performed in adult patients after MHI is relatively high. S100B could also be useful in rural hospitals where no CT scan is available and in the management of ED overcrowding.

Radiation from CT scans contributes to about 2% of all cancers in the US.³ Additionally, repeated exposure to CCT is associated with an increased risk of cataracts.³⁷ Many older patients are “frequent fallers” and, after each fall leading to hospital admission, radiography and/or CT scans are frequently performed.²³ Therefore, reducing unnecessary radiation exposure is a major health concern in the future.

The introduction of S100B as a reliable, examiner-independent parameter to improve the indication for CCT scans has already been recommended, among other suggestions, in the above-mentioned Scandinavian Guidelines in patients after MHI.³³ In patients with a GCS score of 14 and no risk factors (like anticoagulant therapy or age older than 65) or GCS 15 with loss of consciousness or vomiting and no other risk factors, S100B should be used.

Of the 782 patients, 50 (6.4%) had positive CCT scans, a finding that was—surprisingly—consistent with the results of other studies in which most of the patients included were younger than 60 years.^{2,38} Additionally, about 80% of our patients were on medication with PAIs. In our study, older patients who had received PAIs had an even lower rate of intracranial hemorrhage than those who had not received PAIs. The difference is not statistically significant (5.9% vs 8.6%), but it confirms the results of the study by Spektor et al. showing no statistically significant difference in the frequency of intracranial bleeding between patients who had received low-dose aspirin and those

TABLE 4. Intracranial injuries and CCT findings in 50 patients with bleeding from MHI

Traumatological CCT Findings	No. (%)
Epidural hemorrhage	0 (0.0%)
Subdural hemorrhage	24 (48.0%)
Subarachnoid hemorrhage	12 (24.0%)
Intracerebral hemorrhage	14 (28.0%)
Total	50

without.²⁶ The similar rate of patients with positive CCT scans in our special cohort compared with other studies is a strong argument against the common assumption that older patients and those receiving PAIs have a higher risk for intracranial bleeding than younger patients and those without PAIs. Therefore, the usual clinical practice, which is to perform CCT after MHI, particularly in all older patients and in all patients treated with PAIs, should be reconsidered. In this context, the recommendation from the Scandinavian Guidelines that patients with MHI whose GCS score is 14–15 and who present with the combination of age older than 65 years and antiplatelet medication should undergo CCT, has to be rethought or clarified.

There is an ongoing medical discussion whether a so-called “early” CCT scan is reliable in diagnosing intracranial hemorrhage after MHI, particularly in older patients with antiplatelet therapy.^{20,28} We regard a CCT performed within the first 3 hours after the injury as an “early” CCT. In a prospective analysis of older patients with MHI who were taking low-dose aspirin, Tauber et al. found, in patients with initially negative CCT, a 4% rate of delayed hemorrhage on repeat CCT.²⁸ In our study an “early” CCT (within the first 3 hours after the trauma) was performed in 128 of the 782 patients (16.4%); CCT was positive in 23 and negative in 105. We made a sensitivity analysis in which we classified the negative CCT scans that were obtained within the first 3 hours after the event as “unverified” instead of “negative.” This analysis was performed using the method proposed by He and McDermott and using bias-corrected and accelerated bootstrap confidence intervals.^{5,10} The results of the S100B test using the proposed cutoff remained quite similar after applying this statistical method in our study: NPV 99.6% (CI 98.8%–100%), PPV 11.5% (CI 8.9%–14.3%), sensitivity 98.3% (CI 94.6%–100%), and specificity 35.8% (CI 32.0%–39.6%). We can conclude that the results presented in our primary analysis are not significantly influenced by the fact that our CCT scans were performed both as “early” and “late” scans. To avoid further discussion about the time point of a reliable CCT scan after trauma, we also extrapolated our results by defining CCTs performed within the first 12 hours as “unverified.” This analysis yielded the same NPV of 99.6% (CI 98.3%–100%).

The objective of our study was to help physicians performing the initial management of MHI in older patients decide which patients should undergo CCT, which should be admitted, and which should be discharged. For the first time, a brain biomarker, S100B, can be considered in the difficult process of evaluation and decision making

TABLE 5. S100B and CCT findings in 782 patients with MHI*

S100B Level	CCT Negative†	CCT Positive†	Total	Predictive Value
<0.105 µg/L (negative)	258	1	259	NPV 99.6% (CI 97.9%–99.9%)
≥0.105 µg/L (positive)	474	49	523	PPV 9.4% (CI 7.2%–12.2%)
Total no.	732	50	782	

* S100B proves to be a good negative predictor for intracranial hemorrhage after MHI in patients older than 65 years and in patients being treated with PAIs.

† For negative CCT findings, specificity was 35.3% (CI 31.9%–38.8%); for positive CCT findings, sensitivity was 98% (CI 89.5%–99.7%).

regarding older patients and in those with antiplatelet therapy. Using a cutoff of 0.105 µg/L and an interval of less than 3 hours between trauma and blood drawing, S100B has been shown to be especially suited to predict the absence of pathology on CCT. The only patient observed in this study with an intracranial hemorrhage and negative S100B had a concentration slightly below the cutoff (0.094 µg/L) and no need of neurosurgical intervention. The NPV of S100B is 99.61%. This negative prediction is of particular importance because all the other risk factors are of a positive predictive nature. In combination with conventional clinical decision criteria, measurement of S100B allows the reduction of CCT by approximately 30% in older patients with MHI who fulfill the described criteria. Of our CCT-negative patients, 64.7% were S100B positive. The low PPV (9.4%) means that a positive S100B cannot be used for further clinical decision making.

A few limitations concerning our results should be considered. First, we have no data concerning the outcome of our CCT-negative patients beyond the observation period. The median interval between injury and CCT was 15:40 hours, and the median observation period was 31:37 hours. We cannot rule out hemorrhages that might have occurred after the end of observation. However, neurological deterioration would have been a reason for readmission. Second, the history of antiplatelet drug use is not very reliable in older patients, and aspirin resistance is a frequently observed multifactorial phenomenon.³⁵ The effects of aspirin and clopidogrel have been shown to be highly variable between individuals. Furthermore, medication interaction, absorption, and metabolism are factors that can significantly impact bleeding risk and platelet function.¹⁹ Platelet function testing was not done in the context of our study.

Conclusions

We can conclude that S100B levels below 0.105 µg/L can accurately predict a normal CCT scan after MHI in older patients and those on antiplatelet medication (low-dose aspirin and/or clopidogrel). Combining conventional clinical decision criteria with measurement of S100B provides useful information for the management of MHI in these patients and leads to the reduction of CCT scans and admissions for observation by approximately 30%.

In times of increasing concern about overdiagnosis and overtreatment, this is of special importance with regard to radiation-associated health risks and financial burden.

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Author Contributions

Conception and design: Thaler, Schmidsfeld, Gleiss, Mousavi. Acquisition of data: Thaler, Schmidsfeld, Pusch, Pienaar, Wunderer, Pittermann. Analysis and interpretation of data: Thaler, Schmidsfeld, Pienaar, Valenta, Gleiss, Mousavi. Drafting the article: Thaler, Schmidsfeld, Pienaar, Gleiss. Critically revising the article: all authors. Reviewed submitted version of manuscript: all

authors. Approved the final version of the manuscript on behalf of all authors: Thaler. Statistical analysis: Gleiss. Study supervision: Fialka, Mousavi.

Supplemental Information

Previous Presentation

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Correspondence

Heinrich W. Thaler, Trauma Hospital Meidling, Kundratstrasse 37, A-1120 Vienna, Austria. email: heinrich.thaler@auva.at.