CURRENT CONCEPTS OF EDUCATION AND DEVELOPMENT OF THERAPEUTIC EFFICACY IN POLYTRAUMA MANAGEMENT

PhD Thesis

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List of original papers

List of full papers relating to the subject of the thesis

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Advanced Trauma Life Support (ATLS) in Hungary; The First 10 Years.

Bull Emerg Trauma. (2016) 1:48-50. IF: 0.60

Jávor P, Csonka E, Butt E, Rárosi F, Babik B, Török L, Varga E, Hartmann P. Comparison

of the previous and current trauma-related shock classifications - A retrospective cohort

study from a level I trauma centre.

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Csonka E, Tuboly E, Jávor P, Varga E. Figyelemfelhívás magyar polytrauma regiszter

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2

1. INTRODUCTION

1.1. Advance Trauma Life Support (ATLS)

The Advanced Trauma Life Support (ATLS) course supplies its participants with a safe and effective method for the immediate treatment of severe injured patients. It gives a reliable procedure to assess a patient rapidly and accurately and resuscitate and stabilize according the priority simultaneously. Help to determine whether a patient needs exceed the resources of a facility and arrange appropriately for a patient's interhospital or intrahospital transfer. Ensure that optimal care is provided and that the level of care does not deteriorate at any point during the evaluation, resuscitation or transfer process. The ATLS programs are recognized as the standard educational trauma program worldwide. The content and skills presented in this course are designed to assist doctors in providing emergency care for injured patients. The course provides the essential informations and skills for participants to identify and treat life-threatening and potencially life-treathening injuries under the extreme pressures of a fast paced procedures and athmosphere of a trauma room. Upon completing the ATLS course, the doctors will be able to establish primary and secondary survey management of acute life-threatening conditions in a timely manner. Analyzing the datas from World Health Organization (WHO) and the Centers for Disease Controll (CDC) the burden of injury is even more significant, accounting for 18 % of the world's total diseases. The collected data suggest that ATLS has a positive impact on the value of trauma care. Injuries accompanied by massive blood loss are leading cause of death among young adults. Hypovolemic shock is the second main cause of mortality in trauma patients, and the outcome can be improved significantly through early recognition, intravenous fluid resuscitation and blood transfusions. Currently, ATLS program provides well-established guidances for early assessment and initial management of major trauma and suspected hemorrhage by allocating the patients into severity classes I-IV, respectively. Until recently, the earlier guidance proposed the use of vital signs (VS) only, including heart rate (HR), systolic blood pressure (SBP) and Glasgow Coma Scale (GCS) to aid the recognition of shock and estimate blood loss. However, the analysis of the Trauma Register DGU® (Deutsche Gesellschaft für Unfallchirurgie) indicated that the VS-based classification does not reflect the clinical condition accurately. Therefore, the latest ATLS recommendation expanded the assessment criteria with the BD value. BD is a metabolic marker reflecting the acid-base status of the patients and commonly used to assess hemorrhage and its consequences. Several studies have documented its ability to predict mortality and postinjury transfusion requirements and highlighted its role in the early assessment of condition in trauma patients. However, the specificity of BD for hypovolemia prediction is still questionable, since not only metabolic acidosis, but other factors such crystalloids (Lactated Ringer or saline) can also elevate BD. Furthermore, alcohol or drugs, commonly seen in trauma patients, may also diminish its predictive accuracy. Besides, it has been demonstrated that patients over 55 years may have significant injuries and mortality risk without manifest BD alterations.

Medical registries are prospective and systematic collections of clinical, demographic, and other data from patients who meet specific criteria, for pre-defined purposes. Large amounts of clinical and demographic data may be suitable for setting up and validating hypotheses, to design protocols and control their effectiveness, quality control of patient care, to compare the performance of institutions, regions, or countries; to select participants for clinical trials, for prevention purposes or even for the analysis of pre-hospital and rehabilitation phases. The positive impact of trauma registers on the quality of patient care and scientific activity seems to be evident. This is especially true for the treatment of severe injuries (ISS\ge 16), where randomized controlled trials are hard to conduct due to the time factor, the unconscious state of many patients, and the interdisciplinary nature of patient management. The Victorian State Trauma Registry (VSTR) in Australia illustrates well that monitoring patient care via statistics makes it possible to identify systemic problems, thereby provides an opportunity for quality improvement. VSTR's 2-year statistics (2001-2003) showed that one in five injured transport times in the region that did not require a technical rescue exceeded 1 hour; in 60% of individuals with hemodynamically unstable, penetrating trauma, ambulance staff spent more than 10 minutes on site, 48.4% of severe injuries with GCS < 9 mental status did not undergo intubation at the site. In 28.7% of major trauma cases, no complete trauma team alert occurred; furthermore, in 23.7% of head injuries, more than 2 hours elapsed before performing a cranial CT from hospital arrival.

2. MAIN GOALS OF THE STUDIES

Our main goal is to analyze different aspects of education and data collection that could lead to the quality development of trauma care in Hungary. The approach provided by ATLS has become a relevant part of education in the field of trauma worldwide, since it is associated with the decrease in the number of preventable deaths. We aim to emphasize the

importance of organizing courses and actively search for new areas of improvement in ATLS. We also aim to highlight the need for a national trauma register, as unified systematic data collection could lead to better quality control, identification of new predictive parameters, and ultimately better patient care.

- As a first step, in study I., we have provided a brief overview on the ATLS program. Student evaluation and statistical data about the participants were collected throughout the 10-year history of the Hungarian program.
- Then, we set out to examine the predictive power of the currently accepted ATLS classification of hypovolemic shock to confirm or refute the superiority of VS+BD detection over the previously used (VS only) protocol. Thereforein study II. we have conducted a retrospective cohort analysis at a level I trauma centre to compare the VS+BD and VS classifications in terms of their ability to predict mortality. Our secondary goal was to determine the parameters with strong prognostic possibilities in the early assessment phases of the injured. Therefore, the predictive values of HR, SBP, GCS and BD were also calculated.
- Finally, we aimed to highlight the need for a national registry in our country via presenting one mass casualty. In search for new predictive factors, markers of shock and routine labor parameters were collected and analyzed. We aim to demonstrate that isolated cases can draw attention to new contexts and point out new areas of improvement; however, in the lack of possibilities for validation, new ideas cannot become a part of evidence-based medicine. In order to overcome our limitations, the establishment of a national trauma registry is required urgently.

3. MATERIALS AND METHODS

The clinical studies were conducted in accordance with the Declaration of Helsinki and has been approved by the local medical ethics committee at the University of Szeged under reference number 182/2019-SZTE.

3.1. Protocol in Study I.

3.1.1. Study design

The objective of this study is to provide a narrative analysis to explore the association of ATLS courses and participants satisfaction in regards to educational strategy, quality of lectures and skills practices and possible effectiveness and efficiency of the course on trauma care. Secondary data analysis was completed on survey responses from 305 participants of the first 20 Hungarian ATLS courses.

This retrospective study used a secondary data source from the ATLS feedback questionnaires. The survey contained questions that asked participants to identify the level of trauma care center they came from and their speciality fields. Additional survey items asking participants to rate office staff were removed from the analysis, leaving 16 survey items that were retained for the purpose of the study. Five items were grouped to the category of educational strategy and possible future usefulness. Survey items used a variety of categorical measures including yes/no, never/sometimes/usually/always, and not at all/a little/some/a lot. Five items into the category of lectures and six items were grouped into the category of skills practices and simulated scenarios. The overall lectures and skills practices rating survey item used a Likert-type scale of 1 to 5 (1 = worst lecture possible; 5 = best lecture possible) in whole number increments.

3.2. Protocol in Study II.

3.2.1. Study design

The present study is a retrospective cohort analysis at a single, level I trauma centre located in an urban area. The level I qualification is based on national standards regarding the kinds of resources available and the number of patients admitted yearly. The designation criteria correspond to United States of America standards.

3.2.2. Data collection

In the past decades, there were several important changes in emergency trauma guidelines, such as the paradigm shift in fluid resuscitation and the introduction of tranexamic acid. Taking this into account, we decided to analyze data only from the past 5 years, the data were collected between 11 July 2014 and 11 September 2019 from the electronic database (MedSolution) at the University of Szeged. The protocols of emergency trauma care including massive transfusion protocols at the institution have been in complience with the 6

principles of ATLS during the whole study period.

3.2.3. Inclusion criteria

The inclusion criteria consisted of trauma team activation, transport directly from scene, age of 16 years or greater, a detailed documentation including Abbreviated Injury Scale (AIS), Injury Severity Score (ISS), the accurate mechanism of injury and a complete dataset for HR, SBP, GCS and BD recorded at presentation. The activation of the trauma team is based on anatomical and physiological criteria and the mechanism of injury. The age limit of 16 years was selected according to the fact that normal values of HR and SBP by adolescents above that age do not differ largely from the normal values by adults. The recorded variables included the mechanism of injury, the International Statistical Classification of Diseases and Related Health Problems (ICD) codes, vital parameters (HR, SBP and GCS) measured by the trauma team at presentation, BD and 30-day survival.. When patients were discharged from the hospital earlier than 30 days, the follow-up was completed as a part of outpatient care.

Patients who received cardiopulmonal resuscitation on scene or primary survey in another institute were excluded. Additionally, imprecise documentation and missing variables also entailed exclusion.

3.2.4. Patient groups

The ATLS does not explicitly declare whether the worst parameter or a combination of all the parameters should determine the severity class of the patient. Most trauma patients cannot be allocated correctly to the four ATLS severity classes (I–IV) when a combination of vital parameters is assessed. Therefore, the participant's allocation was based on their worst parameter within the VS and VS+BD criteria. Since the current ATLS shock classification does not describe exact values for HR, SBP and GCS, we adopted HR values from the previous ATLS classification and SBP and GCS values from the study of Dunham et al. to make the criteria objective and transparent.

3.2.5. Outcomes

As a primary outcome, we compared the VS and VS+BD classifications with respect to 30-day mortality, taking the close relationship of the severity of bleeding to the risk for adverse outcomes into consideration.

As a secondary goal, we studied the prognostic potential for the individual parameters (HR,

SBP, GCS and BD, respectively) to be able to determine the strongest and weakest predictive factors in the initial assessment.

3.3. Protocol in Study III.

3.3.1. Patient selection and data collection

In our present study, we have focused on patients who suffered severe injuries (ISS \geq 16), but did not need cardiopulmonal resuscitation on scene. According to these criteria, 9 passengers were selected initially. Two patients were excluded due to their age (9 and 12). One person was transferred from another hospital in a later phase of treatment.

3.4. Statistical analysis

In Study I, the results of a detailed questionnaire were evaluated by means of a score system on a scale from 1-5. Descriptive statistics were made and data were presented as mean values.

In Study II, continuous data were expressed as mean \pm standard deviation. Categorical data were expressed as frequency or relative frequency (percentages). Chi-square tests for independence were performed to test the reationship between VS+BD classification result and outcome of mortality. The assumption of chi-square test for independence was slightly violated in the crosstabulation of VS classification result and outcome of mortality, therefore Fisher's exact test was used to test the relationship between VS classification result and outcome of mortality.

Two-proportion Z-test was performed to compare the predictive power of the VS and VS+BD classifications. Binary logistic regression was applied for further analysis between VS+BD classification result (groups 1, 2 vs groups 3, 4) and outcome of mortality, odds-ratio and 95% confidence interval for odds-ratio were calculated.

The predictive performance of individual variables was assessed using receiver operating characteristic (ROC) analysis. Area under ROC curve was calculated for each individual variable (candidate predictors: GCS, HR, SBP, BD). Hypothesis tests for AUC ROC were performed and 95% confidence bounds for AUC ROC were calculated with nonparametric method. A P-value P<0.05 was considered to be statistically significant. All data were analyzed by using statistical software IBM SPSS 25.0 (IBM Corporation, Chicago, IL, USA).

In Study III, data were arranged into a data management software (Sigma Stat 12.0).

Descriptive statistical analysis was performed to characterize our patients based on mean and standard deviation (SD) and for data not following the normal distribution, on median and range. Spearman multiple rank correlation was also performed to find any linear relationship between data obtained and then Wilcoxon-test was ran to compare parameters determined at 6 h and 72 h. On the next step, primary and secondary outcomes will be included as short-term (1 month) mortality, hospital-and ICU length of stay and SIRS, acute organ dysfunctions, multiple organ failure and sepsis.

4. RESULTS

4.1. Study I.

Nearly 50% of the participants came from either a university hospital or the National Institute of Traumatology, thus representing the high levels of Hungarian trauma care. We hope to further spread the concept amongst the lower level centers. Over 80% of the participants were working in the specialty fields of orthopedics & trauma, traumatology, anesthesiology & intensive therapy, and emergency medicine, showing the major specialties participating in trauma care in the Hungarian trauma settings. An educational activity is very accurately judged by the satisfaction of the participants, thus it is very important for every ATLS center. This feedback can assure that the quality of the course remains on the desired level. All of the 305 participants responded positive to the question "Have you learned new and useful information?". It shows that a structured educational strategy can be useful to every participant. Similarly, all of the participants responded positive to the question "Does it worth the time spent on it?". As high as 97% of the participants thought that the course did worth the course fee.

The skills practices and simulated scenarios are very important parts of the ATLS course, but it is also very important to keep the lectures on a high level of quality. The lectures are evaluated year-to-year to keep that high level. If scores from all years are evaluated at once, none of the lectures get an average grade below 4.6 on a scale of 5

4.2. Study II.

According to VS, 31.4% of the patients were assigned to class I, 6.4% to class II, 13.5% to class III and 48.7% to class IV. Based on VS+BD criteria, 16.0% of the patients were reallocated to a higher severity class; however, this change affected mostly the low-risk

classes (I and II). 34 patients died within the first 30 days, resulting in a mortality rate of 21.8%.

Both the VS and VS+BD classifications showed a strong relation to mortality (chi-square and Fisher's exact tests P_{VS} =0.0001 vs. P_{VS+BD} =0.000009, respectively).

Through a separate analysis of HR, SBP, GCS and BD, we found that GCS has the highest prognostic power (AUC_{GCS}=0.799, P<0.001; CI [0.722, 0.875]). Derangements in BD and SBP were significant but weak predictors of mortality (AUC_{BD}=0.683, P=0.001, CI [0.576, 0.790]; AUC_{SBP}=0.633, P=0.018, CI [0.521, 0.744]). HR was found ineffective in prognosis (AUC_{HR}= 0.595, P=0.090, CI [0.480, 0.710]).

The binary logistic regression analysis confirmed that the risk for mortality increases massively in the higher severity classes (III and IV) as compared to the less severe ones (I and II).

4.3. Study III.

The most affected body regions were the chest, pelvis and extremities. Pneumothorax occurred in 3 from the 5 included patients. Traumatic Brain Injury (TBI) was present in 2 cases, while only one person had a significant abdominal injury.

Significant negative correlation demonstrated between 6-hour WBC and 72-hour creatinine levels (rs = -0.949; p = 0.0167) and between 6-hour PLT and 72-hour creatinine levels (rs = 0.876; p = 0.0833), these changes may have predictive power when examined in combination.

Examining the change in routine laboratory parameters measured at 6 and 72 hours postinjury over the time interval between the two samples, PLT, WBC, and creatinine levels showed significant changes.

5. DISCUSSION

5.1. Impact of Hungarian ATLS courses on trauma care

As of 2015, Hungary is still one of the only three countries from Eastern Europe to have an ATLS program, the other two countries being Lithuania and Slovenia. The instructor's program is also successfully running with about 25% of the participants showing instructor potential and 3 instructor courses held throughout the years. Szeged is until 2015 was the only ATLS center in Hungary, organizing 2 courses every year for 16 participants a course.

In 2016 launched the second course venue in Budapest to get possibility of 4 courses per year. Since 2013, successful completion of an ATLS course is a prerequisite for the Hungarian state board examination in orthopedics & trauma surgery. Also, as the Hungarian emergency system is shifting to establishing central Emergency Departments replacing the old, separated emergency system for the different specialties, more-and-more residents are going to start in the field of emergency medicine, with the possibility of the ATLS course becoming a prerequisite for the board examination in emergency medicine as well. These two facts indicate that the interest in the course is going to significantly rise in the near future. Investigating the impact of ATLS on the quality of Hungarian trauma care would be very challenging. It is very important to make the idea and concept of the training spread in the Hungarian trauma system. As nearly half of the participants were under 30, and as completion of an ATLS course is now a prerequisite for obtaining an orthopedics & trauma certification, we can hope that the front line of the near future of the Hungarian trauma system will bear the skills and foundations required for a state-of-the-art approach.

Participant's failure is also a very important aspect of a medical educational course. Only a bit over 3% of the participants failed to pass, and less than 10% had to retake either the MCQ or the practice examination. These points to the fact that until recently, taking the course was not obligatory, thus all participants were motivated. As skills-centered, practice-based, structured education gains more and more territory in both undergraduate and graduate medical education, we hope that we can build on the success of the Hungarian ATLS program and that these efforts lead to further improvement of the Hungarian trauma system.

5.2. Comparison of the current and previous ATLS classifications

This study was designed to investigate the previous, VS-based and the current ATLS classifications and the prognostic power of the parameters. Both classifications were highly effective in predicting mortality, with no significant difference between their prognostic values. Therefore, the superiority of VS+BD over the VS classification could not be confirmed.

Some other findings are also noteworthy, as we have demonstrated that more than 90% of all deaths were distributed in classes III and IV. This data underlines the importance of the threshold between classes II and III, where the first derangements in SBP, respiratory rate and urinary output usually occur. According to other studies, the threshold BD value between these two classes (6 mmol/L) shows a notable predictive potential for mortality

and transfusion requirements post-injury. 6 mmol/L is also the threshold from where the administration of blood products is recommended by ATLS. The therapeutic and prognostic relevance of this point questions the reasonability of dividing trauma patients into four different severity groups. Additionally, due to the need for rapid decisions in the emergency trauma setting, the complexity of the ATLS shock classification has already received criticism before its extension with the BD. Based on our study, combining the less severe classes (I and II) and the severe classes (III and IV) could be a legitimate option to increase the practicality of the classification.

As a secondary outcome, the predictive values of the individual variables were evaluated. GCS, BD and SBP showed a significant predictive performance. While GCS displayed a relatively strong relation to the outcome, the relation was weak for BD and SBP. In our study, BD and SBP alone did not appear to have a sufficiently high prognostic potential to be the foundation for the early assessment. According to other studies, SBP is considered to have a poor reliability in the early assessment, since hypotension usually does not occur until the degree of shock is profound. Despite of its strong relation to mortality, GCS can be affected by several factors besides hypotension, such as traumatic brain injury or alcohol intoxication.

Of note, HR did not have a significant relation to mortality in our study. Numerous factors such as anxiety, pain, medication and spinal cord injury can lead to elevated HR, making the specificity of tachycardia for hypotension questionable. Increased HR may also be masked via beta blockers (particularly in combination with Ca2+-channel inhibitors and ACE inhibitors) or physiological bradycardia. Multiple studies pointed out that HR tends to demonstrate a biphasic response to bleeding since the patients develop bradycardia as blood loss becomes profound after initial tachycardia. In our study, the predictive values of the individual variables showed the following ranking: GCS>BD>SBP>HR. The relevant differences between the variables suggest that weighing them and using their combination to allocate trauma patients could potentially increase the accuracy and specificity of the classification for hemorrhage. However, further research with larger sample size is required to elaborate such modifications.

Limitations of this study are coming from its retrospective nature. Although our cohort analysis with the given sample size only has limited value as a validation study, it provides original research information in a controversial topic and highlights potential areas of improvement for an assessment tool that is mistrusted by several clinicians.

With regard to GCS upon admission, the concern emerges whether prehospital intubation had a major influence on patient allocation. In accordance with the paramedics protocol, onscene intubation is indicated in case of GCS<8, which already entails the allocation into class IV according to the criteria of shock classification used in our study. Consequently, the distortional effect of prehospital intubation on our results is not likely.

The use of vasopressors occurred mostly in classes III-IV, thus having less influence on our results.

In conclusion, despite the significant relationship between BD and mortality, the previous and current ATLS classifications yielded nearly equivalent predictive performances, thereby rendering the added value of BD to the classification questionable. Undoubtedly, post-injury vital sign values are continuously changing during trauma care and individual reactions can vary greatly. Despite these facts, trends may appear in the derangements of physiological variables. In this study, the capability of individual variables to predict mortality followed the GCS>BD>SBP>HR ranking. The role of HR in the early assessment of trauma patients may worth reconsideration in further studies since it does not seem to reflect the clinical condition accurately. Although the ATLS shock classification is not necessarily a pragmatic scale, it has become taught in more than 60 countries, making an impact on the approach of young clinicians to the initial management of the severely injured. Taking these considerations is into account, striving for the further targeted clicinal investigations and the development of the classification may be advantageous.

5.3. Mass casualty accident highlighting the need for a Hungarian trauma registry

Our current study is a call for the establishment of a national trauma registry in Hungary. In order to demonstrate the potential in having a registry, we presented one mass casualty and raised attention to new probable predictive factors in trauma that are waiting for validation. Many of the systemic responses to severe injury are already well known. Directly after trauma, classical markers of tissue injury are released, including 'alarm' molecules with high immunomodulatory potential and hyperacute pro-inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), or interleukin-1 β (IL-1 β). The release of these components results in Toll-like receptor (TLR) activation with an effect after 1–2 h. After the hyperacute stage, early or subacute cytokines including IL-6, IL-8 as well as IL-12 and IL-18, chemokines and leukocytes migratory factors drive an exaggerated activation of polymorphonuclear leukocytes, and the increased production of reactive oxygen species (ROS) which both heavily contribute to the clinical outcome. The peak of these responses 13

does not start within the first 4 hours from the initial insult and occurs at approximately 12 hours. Consequently, a blood sampling around the 6th hour seems to be applicable for the analysis of the early stage. It is also widely accepted that the initial pro-inflammatory phase switches later to an anti-inflammatory phases with extended anti-inflammatory cytokine release to facilitate regenerative processes, however the pro-inflammatory and anti-inflammatory forces may ultimately amplify each other, creating a state of increasingly destructive immunologic dissonance. It may lead to severe complications such as SIRS, and the overstimulation may result in early multiorgan failure (MOF) within 72 hours after injury. Hence, we aimed to examine the early and late phases simultaneously in order to find predictive factors for the clinical outcome.

Platelet count and serum creatinine level are widely used predictors for several health conditions. Nouér et al. analyzed patients with multiple myeloma and found that both higher platelet counts and higher serum creatinine levels were accompanied by a higher rate of invasive aspergillosis. In the study of Le et al., thrombocytopenia independently predicted death in idiopathic pulmonary arterial hypertension. Kertai et al. revealed a significant association between postoperative nadir platelet counts, and acute kidney injury, and short-term mortality after Coronary Artery Bypass Grafting (CABG) surgery. In the trauma setting, close to 20 % of the significantly injured develop thrombocytosis according to Salim et al. Elevated platelet count is considered to be associated with increased risk of complications during recovery, but also with a decreased mortality rate and therefore may have overall protective effect.

Through the analysis of the acute and late phases of the injury-accompanied inflammation, we have found a strong relation between total leukocyte and platelet counts, and serum creatinine levels. According to our results, the combination of these parameters might have a predictive potential for unfavorable outcomes after injury. For a comprehensive analysis on a large cohort, the establishment of a national trauma registry is needed.

A registry contains uniform medical and demographic data on individuals who meet specific inclusion criteria. Data are documented in an ongoing and systematic manner in order to serve predetermined purposes. Generally, registries require good planning in order to be successful. The core data set, patient outcomes and the target population have to be clear and unambiguous. As another important aspect, the available financial and human resources must be appraised and the key stakeholders should be identified. Besides these basic consideration, several minor details must be discussed in advance.

6. SUMMARY OF NEW FINDINGS

Our brief overview about the Hungarian ATLS program have shown a high level of satisfaction amongst the participating doctors. Most participants are working in higher level centers. According to the participants the program has good quality. Our study emerged further need to establish at least one more new center to provide the adequate number of courses for every professional interested in it or required to take it.

Our findings provided supportive data for the currently used ATLS shock classification does not appear to be superior to the VS-based previous classification. GCS, BD and SBP are useful parameters to predict the prognosis. Changes in HR do not reflect the clinical course accurately, thus further studies will be needed to determine the value of this parameter in trauma-associated hypovolemic-hemorrhagic shock conditions.

As a result of our investigations, we could underline the need for a national trauma registry in Hungary through presenting a mass casualty, and the thoughts generated by it. Simultaneous changes in early leukocyte and platelet counts, and creatinine levels might have a significant predictive potential for unfavorable outcomes in trauma care according to this isolated case series. However, a structured, consensual way of datacollection and large patient population are required in order to validate such speculations. For this purpose, we suggest the establishment of a national trauma registry in our country. Despite the demanding nature of this project, we believe that our goal can be reached through the collaboration of our clinicians and scientists.

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