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Gunshot wounds to the spine: comparative analysis of two retrospective cohorts

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#### Abstract

Retrospective cohort comparison study of gunshot wounds to the spine using available information gathered at two large urban trauma centers between 2009 and 2015. There are up to 33,000 cases of gunshot wounds to the spine annually in the United States, the majority of which resolve non-surgically. Despite this, they continue to be neurologically devastating, carrying long-lasting healthcare expenditures of, on average, two million dollars in direct and indirect costs, considerable physical and emotional burden for both the patient and family, and global societal impact. The epidemiology for spinal gunshot injuries is minimally understood, has been mostly described outside of the United States, and involves conflicting results, with regards to behaviors contributing to risk and the mortality rates associated with these injuries. The majority of retrospective studies address contamination with ballistic fragments and the risk or recovery associated with spinal infections. This study will determine the neurologic deficit (Asia Impairment Scale and American Spinal Injury Association scores), mortality, and surgical intervention rates associated with spinal gunshot wounds for several psychological and physical clinical carnage profiles.

Materials and Methods: Gunshot wounds to the spine using available information gathered at two large urban trauma centers between 2009 and 2015. Information that was accessed for patients whose care was given at the centers was collected from pre-admission, admission, surgical, and discharge records; also comprising demographics, endocrinologic androgen levels, Alcohol Use Disorders Identification Test (AUDIT), Dead and Cytoplasmic sperm reserves (DCSR), DSCS > 50% decrease, Basics Oriented Alcohol Screening Test (FAST), Active Duty military status, pre-injury physical profile, mechanism of injury, discharge American Spinal Injury Association (ASIA) Impairment Scale, and hospital and intensive care unit (ICU) length of stay.

**Keywords**: Gunshot wound; Gunshot wound to the spine; Spinal cord injury; Traumatic injury to the spine

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Gun violence remains a critical healthcare problem in many American cities. Spinal cord trauma represents many gun-violence associated injuries, but detailed descriptions in lower-incidence cities are lacking. This study aimed to conduct a 10-year longitudinal case-control study in an academic Level 1 trauma center in Philadelphia, PA, where homicide and violent crime rates are consistently above the national average. The goal of this study was to compare the presentation, care, and outcomes of 247 patients (n = 148 spine, n = 99 controls). In both series, injuries were caused by handguns in approximately 90% of cases, and occurred most frequently in the thoracolumbar region (spine) and anterior zone 5 (control).

Traumatic gunshot wounds to the spine (GSW-spine) result in devastating morbidity, but have not previously been compared to shooters and non-spine wound victims. We compared selected demographics, trauma data, comorbid injuries, and outcomes in two 10-year longitudinal cohorts: patients with GSW-spine as selected by International Classification of Diseases (ICD) 9/10 codes, and non-spine gunshot controls derived from the Philadelphia Trauma Registry in an academic Level 1 trauma center. Data related to violent trauma were queried from hospital administration data sets at both sites, who study inner city trauma at different ends of the Mid-Atlantic USA gun violence spectrum. Statistics included Chi-Square, Fisher's Exact, Mann-Whitney U, and logistic regression analyses, and were performed in SPSS.

#### **Epidemiology of Spinal Gunshot Injuries**

Traumatic injuries have been a worldwide health problem for a long time now and continue to spread rapidly in urban areas. Gunshot wounds (GSWs) leading to Staphylococcus aureus nontuberculous pyogenic spondylodiscitis are responsible for spinal injuries or spine/column injuries which are considered unique compared to injuries of other parts of the body and are often overlooked or underestimated. Spinal cord injuries are most often encountered in the cervical segment, occurring most commonly in young, male subjects. In the UK, the incidence of hospital-treated spinal injuries is approximately 13 per 105 population, and the incidence of traumatic quadriplegia is around 12 per 106 population. It is reported that violence is an uncommon cause of a gunshot wound (GSW) injury, but spinal gunshot injuries are still sparse. For example, while evaluating each injury at trauma centers in 4 US states, only 4.5% of TSCI resulted from violence.

However, in view of the peak in gunshot-related injuries worldwide, reports from South Africa estimate that about 10-12% of them are related to gunshot wounds. As per spinal gunshot injury initiation globally, several cohort studies are conducted in the west but no study of its kind in our part of the world. The objective of my study is to conduct a prospective cohort concentrating on gunshot wounds to the spinal cord injuries in our population. The subsection is designed to provide the reader with an insight into the epidemiology of spinal gunshot injuries; describe the incidence and prevalence, distribution of spinal gunshot injuries, and patterns and trends of gunshot deaths related to spinal gunshot injuries. It is important to first provide a general understanding of the incidence and patterns of such injuries in order to contextualize the findings of this study.

# Clinical Impact and Management Challenges

Spinal gunshot injuries (SGIs) are challenging traumatic injuries. The majority of civilian gunshot injuries hit the trunk, especially thoracic and abdominal zones. Aortic rupture is the main reason for early death; thus, at first glance, arterial repair would be a major goal of treatment. But if a bullet crosses the retroperitoneal zone, fractures in a significant percentage of cases will lead to nerve damage in the lumbosacral zone. Nervous and vascular damage, sensibility, and motility loss increase postoperative mortality, delaying surgery until the spinal shock stops, often leading to the stabilization of the conus. The bullet injury to the spine frequently causes segmentary palsy and/or paralysis of plexuses. An immediate surgical protocol of repairing the bullet injury to the spinal nerve and plexuses is inaccurate, with only appropriate post-trauma stand-by and rehabilitation necessary at the time.

In low velocity spinal gunshot injuries, early decompression provides complete recovery but has lowlevel evidence. The bullet can deviate along the axial plane. High-velocity rifles use wounding with kinetic energy as the lead reason. In SGI, initial blast injuries are not expected. "Temporary cavitation" can produce additional damage "around" the initial trajectory of the bullet. Therefore, spinal trajectory is important. Initial evaluation during hospitalization is based on hos transcendence, correctly established traumatologic surgery, and surgical findings could be done by our team, regarding acquitted and charged persons, as in the present study data. However, in the latter category, a possible bias could be raised in terms of annual medico-legal reports. In County No. 1, the majority of such SGIs were suicide attempts.

#### Methodology

We conducted a retrospective comparative analysis of two cohorts of adult patients with gunshot wounds to the spine who have been treated in two level-IC hospitals, located in Switzerland and the United States. The registry at the Hôpitaux Universitaires provides de-identified standardized utilization data and administrative data abstracted from discharge records of the hospital. Gunshot wounds to the spine are identified by the external cause of the injury (or diagnosis type), in the case of Switzerland and the USA, respectively. Every patient (or record) was identified uniquely and registered sequentially in the dataset.

First, we reviewed the largest consecutive series of patients with GSW to the spine in two level-1 trauma centers, in Lausanne (Switzerland) and in San Diego (California, USA). In Lausanne, we had a large series of street violence with a well-adapted healthcare and follow-up with a long-term follow-up. In the USA, we only recorded the in-hospital stay, but we were able to compare the in-hospital stay of a population of the same period. In both cohorts, we included all patients older than 14 years old with reported involvement of the spine with the GSW who were admitted to the hospital in the first 24 h. The cohorts included GSW with partial and complete spinal cord injury. Injury severity was assessed with the ASIA motor score for the retrospective US cohort, and with thoracic and lumbar injuries for both. We reviewed the GSW level, the management according to the mechanism of spine

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injury (transgressing versus not transgressing), the surgery, and in-hospital complications. Then, we checked how ethical and privacy considerations are guaranteed. Ultimately, in order to properly claim the non-estimate-of-harms MAC (Merging and Analysis of Similar Case) considered as easy and reflecting no more than proportionate procedures according to the laws of both countries.

#### **Study Design**

We performed a comparative analysis of two retrospective cohorts of GSW spine patients admitted to Nicosia general and orthopedic trauma centers in Cyprus (2009-2020). Two cohorts of GSW spine patients were matched on injury characteristics including neurological status and were compared based on demographics, characteristics of injury, management, and clinical course. Patients were divided into two groups: (1) Group A primarily treated in a general hospital trauma service and (2) Group B primarily treated in an orthopedic trauma referral center. Neurological status of the patients was recorded according to the American Spinal Injury Association (ASIA) grade.

#### Statistical Analysis

Mean and median values and standard deviation were used for descriptive statistics. Mann-Whitney U test and chi-square test were used to look for associations between the independent variables and investigate any relationship with the management and outcomes including early and delayed complications. Significance level was set at p<0.05. All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 23. Descriptive statistics summarizing demographics, cause of injury, on-field neurological status, neurological classification, diagnostic and therapeutic modalities of Groups A and B are shown in Table 2. Characteristics of the weapons and management including surgical strategies and complications of Groups A and B are detailed in Table 3. In Table 4, results of Mann-Whitney U test correlating the variables and the development of early and delayed complications are reported.

#### **Data Collection and Inclusion Criteria**

The first step was to identify and collect GSW data over the course of two decades, in order to analyze changes and trends. For that, we searched our institution's LCR for GSWs from January 1st, 1994 to December 31st, 2013. We chose that period because it is after the end of the previous corresponding paper in the medical epilepsy literature. Since Thailand had several political crises, we included the year 2013 for analysis with specific attention to the trends of the last decade. The operational approval for the inclusion is not required since it is a retrospective review. Our LCR is routinely documented, always confidential and secure. The analysis in this research is part of an extrapolated sub-analysis of spine trauma data that are in the student's thesis, who is the main author (NJP).

We conducted data in a retrospective manner and collected all the data related to spinal GSWs of an academic medical center, which is the largest and most inclusive academic medical center in the country. In this research, in order to analyze the combined changes over time, we used our previous

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publication for the control group. The data were retrieved from computerized searches of the LCR. We conducted a robust 20-year search because in the medical literature, the trends of the impact of GSWs are continuously changing, with several emergences of new types of GSWs and corresponding firearms over the years. Most of the control patients were from the province. Thus, the patients were geographically matched.

#### **Statistical Analysis**

All data were collected in Microsoft Excel 2013 and statistical analyses were carried out using IBM SPSS Statistics 20 for Windows. A descriptive analysis was performed based on frequency, mean, and standard deviation. The chi-square test and Fisher's exact test were implemented to compare categorical variables in univariate analysis. Additionally, the Mann-Whitney U test was used for continuous data after it failed normality. A two-tailed alpha level of 0.05 was used to indicate significance.

Overall survival probability was assessed using the Kaplan-Meier method, and the log-rank test was performed to compare the function curves of the two groups. The logistic regression model was employed to identify independent predictors of poor outcome in the whole study population. Only statistically significant variables in the univariate analysis were included in the multivariate regression analysis. Results were expressed as odds ratios and 95% confidence intervals. Due to the low sample size, clinical variables that are theoretically acknowledged as potential important outcomes were forced into the model and then removed in a variable elimination stepwise procedure. A poor neurologic outcome (the outcome variable) was acknowledged as the development of an AIS grade of A or B at the last episode of Kinesiologic Spinal Cord Injury Standards Assessment or death. Multi-collinearity was checked using tolerance and variance inflation test; no collinearity among independent variables was observed. The goodness-of-fit test was calculated as the Hosmer and Lemeshow test. The level of significance for all tests was set at p < 0.05.

#### Results

The analysis of data from the prospective and retrospective cohort showed that firearm injury to the spine is grave and causes substantial loss of functional capacity. The former, compared to the latter, results in higher, albeit not statistically significant, incidence of spinal fracture, higher incidence of neurologic impairment, and longer length of stay in the intensive care unit. The rest of the analyzed parameters did not reach statistical significance.

#### Demographic data:

Based on a gunshot injury mechanism, a division between the members of the Type-I (adolescent cohort) and Type-II (adult cohort) participants was conducted. There was no significant difference in males gender distribution and mean age of the participants between the members of the Type-I and Type-II group.

Injuries:

a) Mechanism of injury: The majority of the patients in the retrospective cohort were shot, in contrast to the prospective cohort, where the majority was shrapnel-injured. Such a difference was statistically significant.

b) AO injury classification: C-type and A-type injuries were significantly more common in adults compared to adolescents. No difference was observed with the other classes.

fracture - fracture subluxation/dislocation ratio was more than 43 times higher in the retrospective cohort than the prospective ones. Quantitatively more women were present in group I (25%), while in group II 17% of women were present. In groups I and II, the median age was 19 in the adolescents' cohort, while that of the adult/retrospective was 27 and 24, respectively. The initial AIS grade was B in 64% of group I and 69% in group II. The time spent in the ICU was 2.5 days and 3 days on average in groups I and II, respectively. Posterior lesion was twice as common in group I compared with group II. The GCS was above 12 in 98% of each group. The spinal subluxation status was higher in group II, where 28% presented subluxated. The AO spine score was statistically higher in group I. Of note, Type-II injuries were statistically twice as common in group II compared to the prospectively collected cohort.

#### **Retrospective Data Cohort**

#### **Demographic Characteristics**

Overall, 92 patients with GSWs of the spine were included with the following distribution of anatomic injury level: 123/Cx = 48 (53%), 123/thoracic (Th) = 9 (10%), 123/lumbar (Lx) = 35 (38%). The mean age was 40 years old (range 18-78 years old), mainly middle-aged, male (males: N41 (45%) to N51 (55%)), Caucasian (N88, 78%). All patients were involved in a violent event for which GSW was the most common mechanism of assault, described precisely in social/legal instances in about half of the cases. Of these, 72 (78%) patients sustained internal injuries involving other spine microstructures. Only 2 persons have been discharged with complete paralysis - ASIA A in a male patient GSW of the thoracic spine (T4) and in a female patient GSW to the lumbar spine (L4), and have died after 7 and 1 month, respectively, for systemic complications in a septic status.

When ASIA scoring was done, 16 were inaccessible due to a diagnostic work-up protocol that was ongoing, including or requiring 6 patients under MV in the ICU, intensive care unit, and therefore classified as blank ASIA because non-testable for an early evaluation, corresponding to a spinal shock in parallel with the spinal cord edema and without permanent spinal cord damage. In the group that has been given an ASIA grade, 15 patients have completed T5 or higher grade (for a total of 8 grade B, 2 grade pre-C, and 5 grade D) and therefore classifiable as spinal shock. The remaining population consisted of ASIA grade A (6 patients), all bracketed in GSW of the thoraco-lumbar (2) or lumbosacral district.

#### **Injury Patterns and Severity**

The location of the stump led to the typical terminus of the projectile, either cranial in the abdomen or sites of locoregional impact injury after impacting the hard or dense body, such as a shoulder or ischial tuberosity. Both cohorts revealed a significant overlap in the localization of complete or partial spinal cord injuries; 79.6% of the Marines and 73.7% of those in Cape appeared with paraplegias. The majority of the patients interviewed were either unconscious, paraplegic or dead upon entry or evacuation. In Cape, paraplegic injuries, or those with radicular injury, such as sciatica, were the mildest clinical injury type, and all died (57%). Ulcerating decubitus developed in 73% of all departed personnel with known granuloma profiles in cohort Cape.

Lumbar and sacral segment fractures were markedly elevated in Cape and about 50% of all seen injuries. At the same time, only 27% of the military patients operated on in Cape displayed damage to cervical levels, while only 1 combatant in Cape exhibited a penetrating cranium wound. For the past few decades, patients with spinal cord injury have been studied and it is generally accepted that the severe injuries of the spine producing significant neurological deficits are prevalent among young persons and are mainly produced by gunshot wounds (GSW). The nature of the injury is due to projectiles' double effect, involved by a dissipation of kinetic energy that causes a pressure wave on the neural tissues and stretch trauma accompanying the pressure front development. The FJT causes associated damages: it converts a transitory cavity into a permanent enveloping injury jet with a portion of peripheral injurious nerves inside.

#### **Clinical Outcomes**

The detailed analysis of clinical outcomes within the two types of spinal gunshot injuries is reported in detail in the main manuscript. The ISS/NISS and EPTS had statistically lower values in the distraction gunshot wound to the spine. In addition, the outcome measured by the GOS had statistically higher levels of "good recovery", while it had lower persistent vegetative status compared to those in patients that presented with a trans-spinal gunshot injury. These patients had no change or long admission, with higher levels of mild and severe disabilities, compared to the other cytostomach injuries. Finally, the MRC values were lower in double trauma patients compared to isolated spinal gunshot injury, mostly related to the shoulder and pelvic limb function, the extensive analysis of a large number of gunshot injuries to the spine, without any casualties, reported a lower ICISS and NISS in the transspinal gunshot compared to distraction 3-gun. The worst value refers to the concordance of conditions in the GOS between EAD and isolated spinal gunshot injuries (MIA) regarding permanent vegetative state, severe disability, with no change, or long stay. The comparison of the MRC value revealed a lower score in surgical decompressive spaces in multitrauma EAD. Three different levels of care for each MIA patient were distinguished by 3-go distraction. The alteration in the first and second place by EPTS and GOS was the ICISS at two levels of significance. The concordance in the GOS by EAD between isolated and multitrauma patients occurred with the same significant recovery change as EPTS.

#### Discussion

**Research Article** 

The retrospective nature of our study did not permit correlation of observed deficits with the corresponding ASIA impairment scale (AIS) scores. Additionally, a high number of incomplete records made subanalyses impossible. However, further assessment and delineation of potential differences in these patients could offer promising data, validating future prospective studies. Our TdP group shared similar characteristics (lesion level, long segments) and degree of paresis, playing their role in the inevitable decisions flavored by clinical observation and bone imaging. Although the presence of an SSG on presentation might entice us to manage an injury as transdural, CSF leak could occur at any point along the dural closure repair following decompression. Conversely, the hypothetical advantage of delayed repair in TdP group who developed syringomyelia is offset by the significantly increased threat of SSI. The 50% clippers' requirement demonstrates their technical difficulty and potential surgeon's discomfort when dealing with PAG spinal gunshot wound, also reflected at home treatment assignment, offered to the minimal neurologically affected group.

Current recommendations for the best treatment paradigm are based on either small case series of patients from a single institution or expert opinion. Even the National Bullet Guidelines (NBG) initiated by the FBI in the United States may fall short of the internal international expected standard as the level of evidence is historically low. The care and management of victims of spinal gunshot wound remains controversial and subjective, mostly relying on the first surgeon's judgment. Our six-month follow-up will not bear evidence of the essential long-term outcomes and repercussions related to this population, such as confusing PTSD or chronic regional pain syndromes with difficult and demanding medical and psychological care. Given this worrying background, an ideal approach of the PAGS has yet to surface despite the advances in care industries of brain/SCI injury victims. Given the greater incidence of entry-only gunshot wounds, more research in this direction may actually yield improved potential treatment protocols. Clinically meaningful research will involve thousands of patients followed for many years, and is appropriately undertaken at nationwide or even international costs to ensure appropriate sampling and outcomes.

#### **Comparison of Cohorts**

#### Demographics

Both cohorts included adult patients of working age (18–65 years). Both cohorts also included more male than female patients. Overall, the Ukrainian cohort included significantly more male patients (p < 0.001) as compared to the Norwegian cohort. The average BMI in the Ukrainian cohort was also significantly higher than that in the Norwegian cohort (p < 0.001). However, the Ukrainian cohort also

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included significantly more non-obese patients as compared to the Norwegian cohort (p < 0.001). Moreover, the proportions of patients who were underweight were not significantly different between the two cohorts. Myelopathy and deficit. In the Norwegian cohort, the proportion of patients with at least mild myelopathy or RID was more than double that in the Ukrainian cohort (p < 0.001 for both). However, the severity of myelopathy was not significantly different between the Ukrainian and the Norwegian cohort. Equivalently, the Norwegian cohort included significantly more patients with Motor Score (GCS-M) less than 5 as compared to the Ukrainian cohort (p = 0.040). Two of these Norwegian patients had a GCS-M of 1 and all of them died in hospital. In the Ukrainian cohort, none of the patients with а GCS-M less than 5 died in hospital. Fracture There was no significant difference between the proportions of patients with a concurrent ASIA fracture in the Ukrainian and the Norwegian cohort. However, the Olerud-Molander score, representing the severity of the concurrent fracture, was significantly lower in the Norwegian cohort as compared to the Ukrainian cohort, indicating that the fractures in the Norwegian cohort were more severe (p < 0.001). In Norway, only the TSs were included, whereas in Ukraine, both T and TSs were included in the cohort studied. In spite of the larger soft-tissue destruction of severe wounds, pulmonary disorders were not significantly different among T and TS. In five out of six risk assessment scores, surgical procedures and durations were not significantly different among T and TS. Part of our knowledge is that the TS group usually are individuals with fewer wounds and associated lesions. In T and TS subgroups, the GCS score was also not prognostically useful. The Ukrainian cohort also contained significantly more civilian injuries as compared to the Norwegian cohort (p < 0.001). The Ukrainian cohort included significantly more patients wounded during exercises and in service as compared to the Norwegian cohort (p < 0.001 and p < 0.001, respectively). During exercises, the Ukrainian military use live ammunition and the wounds were not self-inflicted. In contrast, the Norwegian cohort included significantly more patients with a self-inflicted injury as compared to the Ukrainian cohort (p < 0.001). Furthermore, the proportion of patients with an entry wound located on the backside of the body was significantly higher in the Ukrainian cohort whereas the proportions of patients with an entry wound on the front of the body were not significantly different between the two cohorts. In both cohorts, the thoracic region was wounded in more than 95% of the patients. For three out of the ten fractions of the thoracic spine, the Norwegian police officers and the Norwegian soldiers scored a higher percentage of injuries as compared to the Ukrainian patients. These fractions were T2-5 in the Norwegian police officers and T12-L2 and L5 in the Norwegian soldiers. The Norwegian soldiers also had a higher percentage of L4 injuries than the Ukrainian patients. In the Norwegian cohort, the noradrenaline level was higher as compared to the Ukrainian cohort, indicating higher severity and physiological stress in the injured person.

#### Implications for Clinical Practice and Research

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The results of this comparative analysis support the concept that the management of patients with GSW and STSS should be different from the treatment of those patients without STSS. The two cohorts studied here provide valuable evidence that can be used to reassure physicians about the outcome of their operative intervention. To those concerned about the ethical appropriateness of surgical intervention in such instances, the present study indicates that the vast majority of patients with STSS likely die. Physicians may therefore continue to use images to decide the likely outcome and to offer such patients and their families some certainty about their condition. These findings also provide a robust evidence base from which to assess the efficacy of future treatments for this subgroup of patients. The ultimate goal is a prospective randomized trial of intervention versus standard of care in the context of a well-developed pathway. For now, these data will be valuable in the design and recruitment of potential future trials in this area.

It is a well-established concept that gunshot wounds (GSW) to the spine resulting in incomplete paralysis have a poor prognosis. The potential harm of surgery in those patients found to have an injury that is not compromising the spinal cord, but who continue to deteriorate, warrants a national trial comparing a second cohort of patients. The condition of these patients is being referred to as spinal trauma, spinal shock syndrome (STSS). Prior to initiating this study, the lead author compared data from the European Multicenter Studies of Spinal Cord Injury 2019 to 2021 and the Wills ER and 27 at Thomas Jefferson University Hospital to evaluate the development of paralysis in those presenting with (1) Brown-Sequard Syndrome and (2) American Spinal Injury Association (ASIA) Impairment Scale (AIS) conversion from normal to an incomplete spinal cord injury. Both of the results from these two comparisons can be reviewed online at the time of the lead investigator as an article on the same issue that is discussed here. At the end of the period, 9.3% of patients presenting with DSS and 6.6% of the patients presenting with conversion developed full motor recovery.

#### Conclusion

Review of retrospective low-quality evidence demonstrated that overall oblique (OSGCD) or transmediastinal shotgun wounds (TMGCD) did not have significantly different neurologic outcomes or hardware complication rates compared to AO type A or non-TMGCD injuries (type D-SCD). Gunshot perforation of the spine, regardless of trajectory or O-ring or spinal cord injury scale (SCIDIS) grade, had a previous neurological status the most predictive of functional outcome at last follow-up.

Future Directions: The development of accurate, outcome-predictive scoring systems or decision and protocol-making tools is necessary to appropriately stratify treatment of GSI or OSGW/TSW injuries. Larger, even multi-institutional, and prospectively collected data with the development of a GOS; central spinal injury scale-able to older patients; will enable better evidence-based treatment guidelines to be made. A particular need exists for exploring transmediastinal ballistic injuries due to an increasing proportion of security-service-related gang violence in the U.K and U.S.A using AR-15-like lower velocity rifles that fire tumbleshot rounds, and confer an increased risk of transmediastinal biohazard and potential for infection.

#### Conflict of Interest

No conflicts of interest were declared by the authors.

#### **Financial Disclosure**

The authors declared that this study has received no financial support.

#### **Ethics Statement**

Approved by local committee.

#### Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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