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Multicenter observational study on practice of pre-hospital management of hypotensive trauma patients: the SPITFIRE study protocol

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ABSTRACT

Introduction Major hemorrhage after injury is the leading cause of preventable death for trauma patients. Recent advancements in trauma care suggest damage control resuscitation(DCR) should start in the prehospital phase following major trauma. In Italy, Helicopter Emergency Medical Services(HEMS) assist the most complex injuries and deliver the most advanced interventions including DCR. The effect size of DCR delivered prehospitally and survival remains unclear however.

Methods and Analysis
This is an investigator-initiated, large, national, prospective, observational cohort study aiming to recruit >500 patients in hemorrhagic shock after major trauma. Primary objective is the exploration of the effect size of the variation in clinical practice among Italian HEMS crews on the mortality of hypotensive trauma patients. The primary outcome measure will be 24 hour, 7 and 30 day mortality. Secondary outcomes include: association of prehospital factors and survival from injury to hospital admission, hospital length of stay, prehospital and in-hospital complications, hospital outcomes; use of prehospital ultrasound; association of prehospital factors and volume of first 24-hours blood product administration and evaluation of the prevalence of use, appropriateness, hemodynamic, metabolic and effects on mortality of prehospital blood transfusions. Inclusion criteria: age>18 years, traumatic injury attended by a HEMS team including a physician, a systolic blood pressure<90 mmHg or weak/absent radial pulse and a confirmed or clinically likely diagnosis of major hemorrhage. Prehospital and in-hospital variables will be collected to include key times, clinical findings, examinations and interventions. Patients will be followed-up until day 30 from admission. The Glasgow Outcome Scale Extended will be collected at 30 days from admission.

Ethics and dissemination
The study has been approved by the Ethic committee “Comitato Etico di Area Vasta Emilia Centro”. Data will be disseminated to the scientific community by abstracts submitted to international conferences and by original articles submitted to peer-reviewed journals.

Study Registration NCT04760977

STRENGTH AND LIMITATIONS

- This is the first attempt to run a nationwide prehospital study in Italy aiming at describing the current clinical practice on prehospital damage control resuscitation of hypotensive trauma patients.
- The main strength of this study relies on its inclusive approach, aiming at recruiting a large number of patients from any region in the country. This will provide a detailed description of patient characteristics, management and their association to clinical outcomes.
- Due to the observational nature of this study we will not be able to confirm causation between prehospital damage control resuscitation and improved outcomes. This work will serve as a founding basis to design future targeted randomized control trials.

INTRODUCTION

Background and Rationale

Major hemorrhage after injury is a global health burden and remains the leading cause of immediate and early preventable death for trauma patients.[1] Traumatic bleeding has challenged civilian and military health systems for many years with extremely high mortality rates.[2] Over the past decade, trauma resuscitation practice has changed from large-volume fluid replacement targeting perfusion to “damage control resuscitation” that prioritizes early correction of coagulation abnormalities.[3-7]

Damage control resuscitation (DCR) was introduced in 2007 after the earlier discovery of acute traumatic coagulopathy, aiming to protect the ability of the patient’s blood to form a clot during the acute bleeding episode.[8] While previous transfusion protocols were focused on correcting coagulation deficiencies after a massive red blood cell (RBC) and crystalloid transfusion volume, in contrast, prevention of coagulopathy is the priority in the new major hemorrhage protocols. The principles of the DCR are early hemorrhage control, permissive hypotension, prevention of dilutional coagulopathy and the identification and rapid treatment of any trauma-induced coagulopathy. Thus, evolutions in trauma care were the introduction of balanced resuscitation with blood products (plasma, RBC, platelets, or, if available, even whole blood),[9] early administration of tranexamic acid (TXA) for the treatment of hyperfibrinolysis,[10] correction of coagulopathy with targeted administration of clotting factors (based of point-of-care clotting diagnostics as thromboelastometry) and early transfusion strategies that brought blood products into the prehospital phase.[11-15] Improved survival from such strategies has been reported in both military and civilian settings.[16-19] Projection of blood products into the prehospital phase of trauma care is intuitively attractive as it reduces time-to-transfusion and improves prehospital survival. However, the use of PHBP is both logistically challenging and resource-intensive, and is not without risk. Effective delivery may require significant performance improvement in prehospital services. Moreover, a substantial benefit on long-term mortality is not yet clear.[20]

In Italy, there are 55 Helicopter Emergency Medical Service (HEMS) bases currently active. HEMS are managed by dispatch centers that are set up on a regional and geographical basis that often correspond to a Level 1 Trauma Center Hospital. HEMS teams usually include one or two pilots, one doctor, one or two nurses, and when a Search and Rescue configuration is in operation an alpine rescue technician. 24 of the 55 HEMS bases work around the clock covering night shifts, while 31 are day-limited. Unfortunately, it is not possible to provide overall data on HEMS interventions throughout Italy as there is no national patient registry. Many systems have a particular configuration either for personnel, logistics, and clinical procedures and no national clinical guidelines or indications exist. Nevertheless, it is estimated that the case volume amounts to about 700 missions per year per base and a nocturnal overall activity of around 7-8%.[21] In October 2020 Bologna and Grosseto HEMS became the first Italian civilian prehospital service to routinely offer prehospital red blood cell transfusion (phRTx). To our knowledge, selected HEMS teams are the only services currently carrying blood products outside the hospital in Italy. To date, we are aware that four HEMS bases in Italy are currently carrying prehospital blood products,

through different configurations and availability, red blood cells, pre-thawed plasma, fibrinogen concentrate and prothrombin complex concentrate are in use (Bergamo, Bologna, Foggia and Grosseto HEMS bases).

Experts in the field have called for prospective studies to improve the knowledge on prehospital trauma resuscitation and, in particular, the role and effects of prehospital damage control resuscitation strategies as per the early administration of blood products [12,22-25] or selected diagnostic procedures such as the delivery of prehospital ultrasound.[26,27]

A significant component of the trauma system method is a trauma registry (TR), which is a comprehensive repository of information on the victims of injuries. TRs allow the monitoring and benchmarking of patient care with the ultimate aim of improving and reducing variability of trauma management across a complex national system.[28] This observational study was designed to be a registry of the sickest injured patients attended by HEMS throughout Italy. Although it is focused on bleeding trauma patients it has the potential to develop into a full national HEMS patient registry.

Aim and Objectives

This is the first attempt to conduct a national multi-center study describing the current prehospital clinical practice, and its impact on in-hospital outcomes. The primary objective of the SPITFIRE study is the exploration of the effect size of the variation in clinical practice among Italian HEMS crews on the mortality of hypotensive trauma patients.[29] The primary outcome measure will be 24 hour, 7 day and 30 day mortality.

Secondary objectives are:

- Association of prehospital factors and survival from injury to hospital admission, hospital stay, hospital length of stay, prehospital complications, in-hospital complications and hospital outcomes.
- Evaluation of the prevalence of use, sensitivity, specificity and effects of prehospital eFAST on patient survival and effects on in-hospital pathways.
- Association of prehospital factors and volume of first 24 hours blood product administration.
- Evaluation of the prevalence of use, appropriateness, hemodynamic, metabolic and effects on mortality of prehospital blood transfusions
- Evaluation of 30 day functional status

Finally, the study data set will be used to prospectively test a previously validated optimal treatment bundle designed to minimize 7-day mortality in hemorrhagic shock using machine learning[30]

METHODS AND ANALYSIS

Study Design

We have designed an investigator-initiated, large, national, prospective, observational cohort study aiming to recruit >500 patients in hemorrhagic shock after major trauma.

Patient and Public Involvement

Patients and the public have not been involved in the study design or in the recruitment and conduct of the study.

Setting

Italy. As of December 2021 a total of 55 HEMS bases are operating in the country (50 all year-long and five seasonal, to serve tourist / holiday peaks). Study investigators (MT, LC) performed an extensive research to obtain email addresses of local air ambulance coordinators. As soon as contact details were obtained a standardized invitation email was sent to representatives of each service, with regular interval reminders encouraging study participation.

Currently 22 bases have agreed to participate and are at various stages of study activation, with 15 actively recruiting patients (Bologna, Pavullo, Grosseto, Massa, Torino, Alessandria, Borgosesia, Cuneo, Udine, Trento, Bolzano, Bressanone, Lasa, Pontives and Treviso).

Recruitment for this study started on January 1st, 2021 and is expected to last a minimum of three years. Additional HEMS bases are encouraged to join the study at any time. Upon requests from candidate centers, a copy of the study protocol and eCRF is sent out for assessment. Geographical distribution of participating centers as of February 2022 is presented in Figure 1.

Participants

Inclusion criteria for this study are chosen apriori based on previously published research protocols and trials investigating prehospital major trauma managed by HEMS and prehospital fluid delivery.[22,31,32]

All patients fulfilling the following inclusion criteria will be recruited:

1. Age > 18 years,
2. Have sustained a traumatic injury and attended by a prehospital helicopter emergency team (PHEM) which includes a physician,
3. A systolic blood pressure <90 mmHg or weak/absent radial pulse during assessment, treatment or transportation to hospital. In case of upper limb injury any contralateral peripheral pulse is considered acceptable,
4. A confirmed or clinically likely diagnosis of major hemorrhage.

The decision to only include Italian pre-hospital helicopter emergency medical services is based on the fact that at the time of writing HEMS teams are the most likely to be exposed to severe trauma patients, deliver the most advanced interventions on scene and are the only (although still uncommon) resources currently carrying blood products prehospitally.

Patients will be excluded if deemed unsalvageable by the HEMS team before starting any resuscitation maneuver.

Variables and source of data

Two major sets of variables will be collected: prehospital and hospital data. Prehospital variables will include mission details, times and mechanism of injury. Clinical assessment and interventions

performed by the prehospital team (including volume of all fluids, crystalloid and colloid and all types of blood products and concentrates). Hospital variables will include emergency department assessment and interventions, results of diagnostic (imaging and laboratory) and therapeutic procedures (including volumes of fluids and blood products). Patients will be followed up at 24 hours, day 7 and day 30 from admission for organ failures and support. Centers will collect the Glasgow Outcome Scale Extended (GOSE) at 30 days from admission. Death happening at any time will be recorded as well as the primary cause of death.

Patient demographics including past medical history, gender, age and comorbidities will be extracted from the patient medical records.

Prehospital and hospital variables will be recorded by treating clinicians or study investigators depending on local clinical practice (some centers may share personnel between the two settings, while others will have separate teams for pre and in-hospital). All clinical evaluations will be performed as per usual standard of care. Variable selection was based on previously published consensus conferences on prehospital data collection.[33-35] Details on collected variables is presented in Table 1 and Table 2.

Table 1. Prehospital Study Variables

Dispatch and Mission	These describe whether the mission includes Search and Rescue (SAR) procedures which are known to increase overall prehospital times; type of dispatch (primary, on-scene crew request or secondary transfer); resources and level of resources on scene (BLS type vs ALS with different configurations); Evacuation to hospital (air vs road).
Times	Key times for the prehospital phase: dispatch center call-connect time ("injury time"), HEMS team with patient time. Hospital arrival time (emergency department triage) will be used to determine the overall prehospital time.

Mechanism of Injury (MOI)	Primary descriptor of the MOI. Road Traffic Accident, Fall (< or > 3 meters), Assault (blunt, penetrating knife or gunshot), Burns, Explosion, Crush, Electrocution, Hanging, Animal bite, Drowning. If RTA furter descriptors are collected: means of transportation, protection (helmet, seat belt, etc), role of injured(passenger, pedestrian, etc), estimated energy (high vs. low). Finally intentionality is recorded (accidental, self-harm, assault, unknown).
HEMS Clinical Examination	Primary clinical assessment including recording of airway, status, lowest SpO2 and arterial systolic blood pressure or radial pulse status. Observed or presumed sites of bleeding (long bones, external compressible hemorrhage, penetrating injury, junctional hemorrhage, (sub)amputation, suspected pelvic fracture, haemothorax, hemoperitoneum. Neurological assessment (first recorded Glasgow Coma Scale, HEMS assessed Glasgow Coma Score and sensory-motor deficits). Ultrasound Extended Focused Assessment with Sonography for Trauma (eFAST) If eFAST was performed and findings.
Prehospital Cardiac Arrest	Whether the patient was at any time in traumatic cardiac arrest and if return of spontaneous circulation (ROSC) was obtained.

HEMS Interventions	Interventions on airways, breathing and circulation including orotracheal intubation or supraglottic device use, use of tourniquets, haemostatic gauzes, pelvic binder, thoracostomies, REBOA or resuscitative thoracotomy and positioning of high flow vascular access. In case of REBOA a subset of data will be collected (Anatomical zone and duration of balloon inflation). Prehospital fluids and blood products Total volume of prehospital crystalloid, colloid, units of prehospital packed red blood cells, grams of prehospital fibrinogen, volume of prehospital plasma and use of clotting factors (prothrombin complex concentrate). Other drugs Induction agents, vasopressors, osmotic and hypertonic fluids, electrolytes, tranexamic acid.

Table 2. Hospital Study Variables

Trauma Team Activation	Data regarding the presence and activation of a trauma team. Also whether a prehospital activation of a massive transfusion protocol is performed.
Emergency Department Clinical Examination	Emergency department clinical assessment including airways, breathing and circulation, estimation of bleeding. Neurological assessment (GCS, pupils and sensory-motor deficits) Temperature at admission.
Biochemical Data	First Arterial Blood Gas performed at hospital admission (pH, PaO_2, $PaCO_2$, HCO_3, lactate, base excess, hemoglobin) ROTEM (if available) INR value at admission aPTT value at admission

Emergency Department Interventions	Interventions on airways, breathing and circulation including orotracheal intubation or supraglottic device use, use of tourniquets, haemostatic gauzes, pelvic binder, REBOA or resuscitative thoracotomy and positioning of high flow vascular access. In case of REBOA a subset of data will be collected (Anatomical zone and duration of balloon inflation). Emergency department fluids and blood products Total volume of prehospital crystalloids and colloids, units of prehospital packed red blood cells, grams of prehospital fibrinogen, volume of prehospital plasma.
Emergency Department Diagnostics	eFAST (if performed and findings) X-Ray (if performed and findings) Computed Tomography (if performed and findings, date and time of CT)
Emergency Department Outcomes	Hemodynamic status at disposition from emergency department (Systolic Blood Pressure, Heart Rate) Lactate and Base Excess at emergency department disposal.
Post-Emergency Department Interventions	The patient pathway following disposition from the emergency department is recorded. Patients might be taken into surgery, angiography, intensive care or die. If taken to surgery or angiography details of the procedure and intraoperative findings are recorded. Intraoperative cardiac arrest and ROSC is recorded.
Scores	Injury Severity Score (ISS) is collected according to international coding standards. Sequential Organ Failure Score (SOFA) at ICU admission SAPS2 at ICU Admission

Intensive Care / High Dependency Unit Admission and discharge	Blood Gasses at ICU/HDU admission Blood Gasses 24 hours from ICU/HDU admission Organ failures within the first 24 hours of hospital admission Type and duration of organ support (mechanical ventilation, tracheostomy, vasopressors, renal replacement) Total number of packed red blood cells during first 24 hours (including prehospital transfusion if applicable) Total volume (ml) of plasma during first 24 hours (including prehospital transfusion if applicable) Total number of platelets pool during first 24 hours (including prehospital transfusion if applicable) Total grams of fibrinogen concentrate during first 24 hours (including prehospital transfusion if applicable) Total volume (ml) of crystalloids and colloids during first 24 hours (including prehospital transfusion if applicable) Further organ failures and surgical interventions at seven days from hospital admission Further organ failures and surgical interventions at thirty days from hospital admission Glasgow Outcome Scale - Extended (GOS-E) thirty days from hospital admission Date, condition and location of hospital discharge Primary cause of death

Data collection and management

Anonymized data will be collected via a web-based secure electronic Case Report Form (eCRF) using the RedCap software (Research Electronic Data Capture, Vanderbilt University, Nashville, Tennessee, USA). The data will be securely stored on the study coordinator local health authority research server (AUSL Bologna, RedCap license from IRCCS Bellaria, Bologna, Italy). Data will be regularly checked for consistency and completeness by the study coordinator and steering committee. Written warnings will be sent to local investigators to correct potential irregularities. All participating centers will join a data transfer agreement to define the terms for data transfer

from the centers to the sponsor. All procedures will comply with the European Union Regulation 2016/279 on data protection.

Study Size

The primary endpoint is to describe the current clinical practice and assess the effectiveness of current practice on patients' 30 days mortality. Major trauma patients experience an overall 20% mortality.[2,9] In order to perform a logistic regression analysis using mortality as the dependent variable, 10 events are needed for each covariate inserted in the model as a rule of thumb. Therefore, a model involving up to 10 covariates will need at least 500 patients.

Plan for Analysis

Patients' characteristics and patterns of lesions will be depicted using descriptive statistics and specific analyses are planned for the primary and secondary objectives. Methodology of analysis is also based on the suggestions from the previous work on Multicenter observational prehospital resuscitation on helicopter study by Holcomb et al. [36,37]

Primary objective

Patients will be divided into two groups based on 30 days mortality, the prehospital and trauma-related variables resulting significantly different between the two groups will be tested as covariates in a univariable logistic regression model. Finally, the multivariable model building will be performed through the least angle regression selection (LARS). Standard errors will be adjusted considering single HEMS bases as clusters.

Secondary objectives

Factor associated with survival to hospital admission will be estimated with a multivariable logistic regression model building as described for 30 days mortality.

Prehospital eFAST accuracy will be tested against CT scan and/or operating room findings of hemoperitoneum. The occurrence of a positive eFAST will be tested as an independent factor in a Cox proportional hazards regression model considering time to definitive diagnostics (CT scan) or treatment (Operating room access). A propensity score matching will be performed to adjust for the covariates that influence the probability of receiving eFAST in the prehospital setting.

A quantilic regression model will be used to test factors associated with the volume of blood products administration during the first 24 hours after hospital admission.

DISCUSSION

Given that the utility of a TR that includes injured patients across a nation-wide trauma system is universally established, we aim to obtain data from a large cohort of trauma patients attended by HEMS. We will provide a detailed description of the patients' characteristics, bleeding trauma patients' management strategies, resource use, system organization and performance and their

correlation to clinical outcomes. The differences in the management of bleeding trauma patients nation-wide, both prehospital and in-hospital, their treatment and therapeutic strategies together with potential outcome association will also be described.

The results generated from this study will complement other large multicentre studies focusing on bleeding trauma patient practice. In addition, for the first time, we aim to collect large-scale national data on trauma resuscitation from the prehospital HEMS phase to the initial in-hospital management.

Bleeding trauma patients is certainly not a naïve research field, however, the nation-wide approach can be considered as the main strength and novelty of the study since it allows to explore the clinical practice in geographical regions characterized by very different health organizations.

Concluding, SPITFIRE study protocol provides a timely and unique opportunity to generate high-quality evidence regarding the prehospital and in-hospital trauma resuscitation. Evidence that we hope will provide useful information for improving the overall management of the bleeding trauma patient nationally and internationally, moreover it will provide useful quality improvement data for prehospital helicopter emergency services around the country and lastly, we hope, it will make a significant difference to influencing future research questions and improving patient care.

ETHICS AND DISSEMINATION

Ethics

The study has been approved by the Ethics Committee “Comitato Etico di Area Vasta Emilia Centro” (approval date 22/10/2020). Each participating center / local Principal Investigator is responsible for obtaining local approval in compliance with the local legislation and rules. The national coordinators will facilitate this process.

Major trauma is unpredictable and often incapacitating and thus immediate prospective informed consent from patients might not be possible. Moreover in the case a patient will retain capacity it is likely that they will need immediate life-saving interventions that cannot be deferred to collect study consent. Consent to participate in the SPITFIRE trial will be sought at the earliest opportunity. Patients or legal representatives will be approached by a local study investigator at a time when they are well and able to receive and process information. All reasonable efforts will be put into place to inform patients or their proxies and to obtain informed consent. In case of patients who die prior to consent being obtained and with no legal representatives recorded data will be included in the study as per indication of the italian data protection authority, section on scientific research (section 5.3.2 Provvedimento del Garante n. 146 del 5 Giugno 2019). Patients can be removed from the study, at their own or their legal representative request, at any time.

The study will be performed according to the Helsinki Declaration and International Conference on Harmonization of Good Clinical Practice.

Registration and Funding

SPITFIRE is registered with clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT04760977)

This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Dissemination

The study results will be submitted for publication in peer-reviewed international journals and presentation at national and international meetings. Study participants will be sent a summary of final results, including details of their local study population. The SPITFIRE steering committee will consider any request on data sharing, on reasonable requests, and decisions will be made after the primary multi-center manuscript has been published.

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Figure Legend

Figure 1 - Current Study Centers (February 2022). Blood drop represents HEMS bases with blood components availability. The Bolzano icon represents the four Alto Adige provincial bases: Bolzano, Bressanone, Lasa and Pontives.

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Contributors

MT and LG designed the study (Principal Investigator and co-PI). MT, LC and LG drafted the manuscript; CL, AG, CAM, VC, SC, DL, JH, GS, CC and GG critically revised the work for important intellectual content; LG and DA are responsible for the statistical and methodological aspects of the study. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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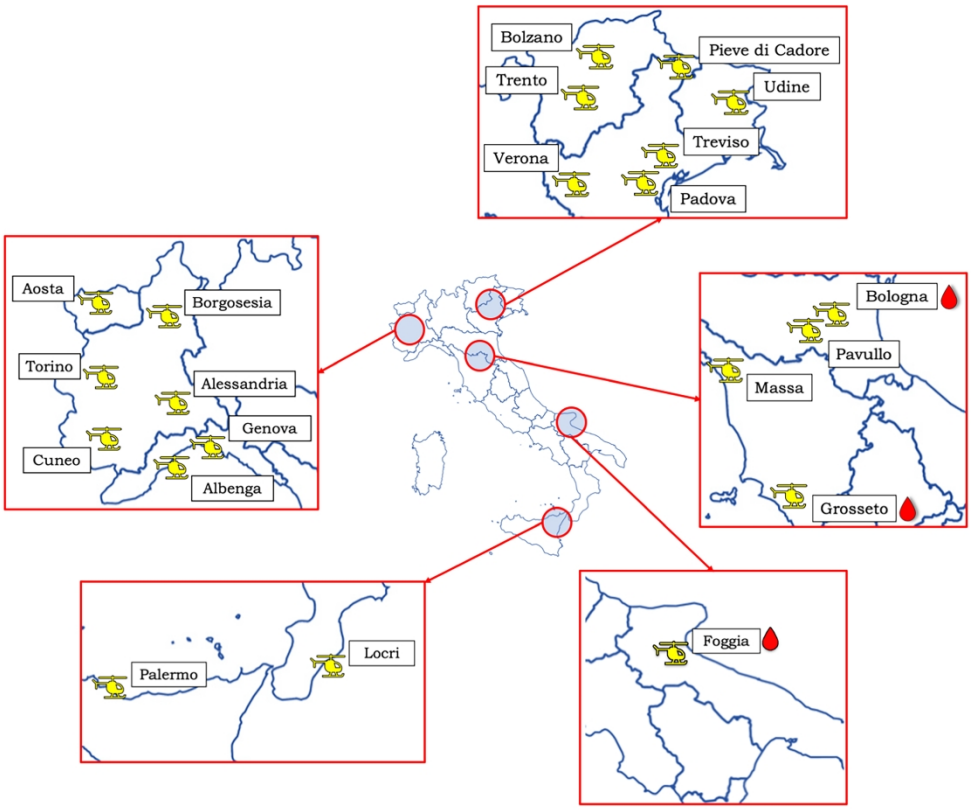
Competing Interests
Prof Holcomb is a consultant with Cellphire, Hemostatics and Arsenal, is Co-founder, Co-CEO and on the Board of Directors of Decisio Health, on the Board of Directors of QinFlow, Zibrio, and

Oxyband and a Co-inventor of the Junctional Emergency Tourniquet Tool. The other authors do not report any competing interest.

Patient Consent
Not Required.

Data Sharing Statement
The SPITFIRE steering committee will consider any request on data sharing, on reasonable requests, and decisions will be made after the primary multi-center manuscript has been published.



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Multicenter observational study on practice of pre-hospital management of hypotensive trauma patients: the SPITFIRE study protocol

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Multicenter observational study on practice of pre-hospital management of hypotensive trauma patients: the SPITFIRE study protocol

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ABSTRACT

Introduction Major haemorrhage after injury is the leading cause of preventable death for trauma patients. Recent advancements in trauma care suggest damage control resuscitation (DCR) should start in the prehospital phase following major trauma. In Italy, Helicopter Emergency Medical Services (HEMS) assist the most complex injuries and deliver the most advanced interventions including DCR. The effect size of DCR delivered prehospitally and survival remains unclear, however.

Methods and Analysis
This is an investigator-initiated, large, national, prospective, observational cohort study aiming to recruit >500 patients in hemorrhagic shock after major trauma. We aim at describing the current practice of hypotensive trauma management as well as propose the creation of a national registry of patients with hemorrhagic shock. Primary objective: the exploration of the effect size of the variation in clinical practice on the mortality of hypotensive trauma patients. The primary outcome measure will be 24 hours, 7 and 30-day mortality. Secondary outcomes include: association of prehospital factors and survival from injury to hospital admission, hospital length of stay, prehospital and in-hospital complications, hospital outcomes; use of prehospital ultrasound; association of prehospital factors and volume of first 24-hours blood product administration and evaluation of the prevalence of use, appropriateness, hemodynamic, metabolic and effects on mortality of prehospital blood transfusions. Inclusion criteria: age>18 years, traumatic injury attended by a HEMS team including a physician, a systolic blood pressure<90 mmHg or weak/absent radial pulse and a confirmed or clinically likely diagnosis of major haemorrhage. Prehospital and in-hospital variables will be collected to include key times, clinical findings, examinations and interventions. Patients will be followed-up until day 30 from admission. The Glasgow Outcome Scale Extended will be collected at 30 days from admission.

Ethics and dissemination
The study has been approved by the Ethics committee “Comitato Etico di Area Vasta Emilia Centro”. Data will be disseminated to the scientific community by abstracts submitted to international conferences and by original articles submitted to peer-reviewed journals.

Study Registration NCT04760977

STRENGTH AND LIMITATIONS

- The main strength of this study relies on its inclusive approach, aiming at recruiting a large number of patients from any region in the country. This will provide a detailed description of patient characteristics, management and their association with clinical outcomes.
- The primary endpoint is to describe the current clinical practice and assess the effectiveness of current practice on patients' 30 days mortality.
- Due to the observational nature of this study, we will not be able to strongly confirm the causal effects between prehospital damage control resuscitation and outcomes. This work will serve as a founding basis to design future targeted randomized control trials.

INTRODUCTION

Background and Rationale

Major haemorrhage after injury is a global health burden and remains the leading cause of immediate and early preventable death for trauma patients.[1] Traumatic bleeding has challenged civilian and military health systems for many years with extremely high mortality rates.[2] Over the past decade, trauma resuscitation practice has changed from large-volume fluid replacement targeting perfusion to "damage control resuscitation" that prioritizes early correction of coagulation abnormalities.[3-7]

Damage control resuscitation (DCR) was introduced in 2007 after the earlier discovery of acute traumatic coagulopathy, aiming to protect the ability of the patient's blood to form a clot during the acute bleeding episode.[8] While previous transfusion protocols were focused on correcting coagulation deficiencies after a massive red blood cell (RBC) and crystalloid transfusion volume, in contrast, prevention of coagulopathy is the priority in the new major haemorrhage protocols. The principles of the DCR are early haemorrhage control, permissive hypotension, prevention of dilutional coagulopathy and the identification and rapid treatment of any trauma-induced coagulopathy. Thus, evolutions in trauma care were the introduction of balanced resuscitation with blood products (plasma, RBC, platelets, or, if available, even whole blood),[9] early administration of tranexamic acid (TXA) for the treatment of hyperfibrinolysis,[10] correction of coagulopathy with targeted administration of clotting factors (based on point-of-care clotting diagnostics as thromboelastometry) and early transfusion strategies that brought blood products into the prehospital phase.[11-15] Improved survival from such strategies has been reported in both military and civilian settings [16-19]. Projection of blood products into the prehospital phase of trauma care is intuitively attractive as it reduces time-to-transfusion and improves prehospital survival. However, the use of PHBP is both logistically challenging and resource-intensive and is not without risk. Effective delivery may require significant performance improvement in prehospital services. Moreover, a substantial benefit on long-term mortality is not yet clear.[20] The recently published RePHILL study investigated whether packed red blood cells and lyophilized plasma was superior to normal saline for improving tissue perfusion and reducing mortality in trauma related hemorrhagic shock [21]. The trial was terminated early due to difficult recruitment during the COVID-19 pandemic and failed to find any difference in the composite outcome (episode mortality and/or failure to clear lactates) between the two treatment arms. The study however presents several complexities such as the inclusion of a broad population of shocked but not necessarily anaemic trauma patients and the use of a composite outcome of episode mortality and/or lactate clearance (two instances that might not be additive per se). Therefore, the results of this trial are difficult to translate to the broad spectrum of trauma related hemorrhages, particularly in exsanguinating trauma patients.

Experts in the field have called for prospective studies to improve the knowledge on prehospital trauma resuscitation and, in particular, the role and effects of prehospital damage control resuscitation strategies as per the early administration of blood products. [12,22-25] Recently the

Italian National Institute for Health (Istituto Superiore di Sanità) published national trauma guidelines suggesting that prehospital blood transfusion should be considered in bleeding trauma patients [26].

In Italy, there are 55 Helicopter Emergency Medical Service (HEMS) bases currently active. HEMS are managed by dispatch centres that are set up on a regional and geographical basis that often correspond to a Level 1 Trauma Center Hospital. HEMS teams usually include one or two pilots, one doctor, one or two nurses, and when a Search and Rescue configuration is in operation an alpine rescue technician. 24 of the 55 HEMS bases work around the clock covering night shifts, while 31 are day-limited. Unfortunately, it is not possible to provide overall data on HEMS interventions throughout Italy as there is no national patient registry. Many systems have a particular configuration either for personnel, logistics, or clinical procedures, and no national clinical guidelines or indications exist. Nevertheless, it is estimated that the case volume amounts to about 700 missions per year per base and a nocturnal overall activity of around 7-8%.[27] In October 2020 Bologna and Grosseto HEMS became the first Italian civilian prehospital service to routinely offer prehospital red blood cell transfusion (phRTx). To our knowledge, selected HEMS teams are the only services currently carrying blood products outside the hospital in Italy. To date, we are aware that four HEMS bases in Italy are currently carrying prehospital blood products, through different configurations and availability, red blood cells, pre-thawed plasma, fibrinogen concentrate and prothrombin complex concentrate are in use (Bergamo, Bologna, Foggia and Grosseto HEMS bases). Complex interventions such as prehospital blood administration require strong governance and documentation. A significant component of any trauma system is a trauma registry (TR), which is a comprehensive repository of information on the victims of injuries including received treatments. TRs allow the monitoring and benchmarking of patient care with the ultimate aim of improving and reducing the variability of trauma management, for instance across a complex national system.[28] With this study we aim at describing the current practice of hypotensive trauma management as well as propose the creation of a national registry of patients with hemorrhagic shock, intending to investigate the relative influence of practice variation on outcomes and ultimately to foster the development of future randomized studies.

Aim and Objectives

This is the first attempt to conduct a national multi-centre study describing the current prehospital clinical practice, and its impact on in-hospital outcomes. The primary objective of the SPITFIRE study is the exploration of the effect size of the variation in clinical practice of damage control resuscitation on the mortality of hypotensive trauma patients.[29] The primary outcome measure will be 24 hours, 7 days and 30 days mortality.

Secondary objectives are:

- Association of prehospital factors and survival from injury to hospital admission,ICU length of stay, hospital length of stay, prehospital complications, in-hospital complications and hospital outcomes.
- Prevalence, Specificity and Sensitivity of clinical examination and prehospital ultrasound when available. [30,31]

- Association of prehospital factors and volume of first 24 hours blood product administration.
- Evaluation of the prevalence of use, appropriateness, hemodynamic, metabolic and effects on mortality of prehospital blood transfusions
- Evaluation of 30-day functional status

Finally, the study data set will be used to prospectively test a previously validated optimal treatment bundle designed to minimize 7-day mortality in hemorrhagic shock using machine learning [32].

METHODS AND ANALYSIS

Study Design

We have designed an investigator-initiated, large, national, prospective, observational cohort study aiming to recruit >500 patients in hemorrhagic shock after major trauma. The actual study start date was May, 1st 2021 and the estimated primary completion date is May, 1st 2025.

Patient and Public Involvement

Patients and the public have not been involved in the study design or in the recruitment and conduct of the study.

Setting

Italy. As of December 2021, a total of 55 HEMS bases are operating in the country (50 all year-long and five seasonal, to serve tourist/holiday peaks). Study investigators (MT, LC) performed extensive research to obtain the email addresses of local air ambulance coordinators. As soon as contact details were obtained a standardized invitation email was sent to representatives of each service, with regular interval reminders encouraging study participation.
Currently, 22 bases have agreed to participate and are at various stages of study activation, with 15 actively recruiting patients (Bologna, Pavullo, Grosseto, Massa, Torino, Alessandria, Borgosesia, Cuneo, Udine, Trento, Bolzano, Bressanone, Lasa, Pontives and Treviso).
Recruitment for this study started on May 1st, 2021 and is expected to last a minimum of four years. Additional HEMS bases are encouraged to join the study at any time. Upon requests from candidate centers, a copy of the study protocol and eCRF is sent out for assessment. The geographical distribution of participating centres as of February 2022 is presented in Figure 1.

Participants

Inclusion criteria for this study are chosen apriori based on previously published research protocols and trials investigating prehospital major trauma managed by HEMS and prehospital fluid delivery.[22,33,34]
All patients fulfilling the following inclusion criteria will be recruited:

1. Age > 18 years,
2. Have sustained a traumatic injury and attended by a prehospital helicopter emergency team (PHEM) which includes a physician,

3. A systolic blood pressure <90 mmHg or weak/absent radial pulse during the primary assessment, treatment or transportation to the hospital. In case of upper limb injury any contralateral peripheral pulse is considered acceptable,
4. A confirmed or clinically likely diagnosis of major haemorrhage.

The decision to only include Italian pre-hospital helicopter emergency medical services is based on the fact that at the time of writing HEMS teams are the most likely to be exposed to severe trauma patients, deliver the most advanced interventions on scene and are the only (although still uncommon) resources currently carrying blood products prehospitally.
Patients will be excluded if deemed unsalvageable by the HEMS team before starting any resuscitation maneuver.

Variables and source of data

Two major sets of variables will be collected: prehospital and hospital data. Prehospital variables will include mission details, times and mechanism of injury. Clinical assessment and interventions performed by the prehospital team (including volume of all fluids, crystalloid and colloid and all types of blood products and concentrates). Hospital variables will include emergency department assessment and interventions, results of diagnostic (imaging and laboratory) and therapeutic procedures (including volumes of fluids and blood products). Patients will be followed up at 24 hours, day 7 and day 30 from admission for organ failures and support. Centres will collect the Glasgow Outcome Scale Extended (GOSE) at 30 days from admission. Death happening at any time will be recorded as well as the primary cause of death.
Patient demographics including past medical history, gender, age and comorbidities will be extracted from the patient medical records.
Prehospital and hospital variables will be recorded by treating clinicians or study investigators depending on local clinical practice (some centres may share personnel between the two settings, while others will have separate teams for pre and in-hospital). All clinical evaluations will be performed as per usual standard of care. Variable selection was based on previously published consensus conferences on prehospital data collection.[35-37] Details on collected variables are presented in Table 1 and Table 2.

Table 1. Prehospital Study Variables

Dispatch and Mission	These describe whether the mission includes Search and Rescue (SAR) procedures which are known to increase overall prehospital times; type of dispatch (primary, on-scene crew request or secondary transfer); resources and level of resources on scene (BLS type vs ALS with different configurations); Evacuation to hospital (air vs road).

Times	Key times for the prehospital phase: dispatch centre call-connect time ("injury time"), HEMS team with patient time. Hospital arrival time (emergency department triage) will be used to determine the overall prehospital time.
Mechanism of Injury (MOI)	Primary descriptor of the MOI. Road Traffic Accident (RTA), Fall (< or > 3 meters), Assault (blunt, penetrating knife or gunshot), Burns, Explosion, Crush, Electrocution, Hanging, Animal bite, Drowning. If RTA further descriptors are collected: means of transportation, protection (helmet, seat belt, etc), the role of the injured (passenger, pedestrian, etc), and estimated energy (high vs. low). Finally, intentionality is recorded (accidental, self-harm, assault, unknown).
HEMS Clinical Examination	Primary clinical assessment including recording of airway, status, lowest SpO2 and arterial systolic/diastolic blood pressure or radial pulse status. Observed or presumed sites of bleeding (long bones, external compressible haemorrhage, penetrating injury, junctional haemorrhage, (sub)amputation, suspected pelvic fracture, haemothorax, hemoperitoneum. Neurological assessment (first recorded Glasgow Coma Scale, HEMS assessed Glasgow Coma Score and sensory-motor deficits). Ultrasound Extended Focused Assessment with Sonography for Trauma (eFAST) If eFAST was performed and findings.
Prehospital Cardiac Arrest	Whether the patient was at any time in traumatic cardiac arrest and if a return of spontaneous circulation (ROSC) was obtained.

HEMS Interventions	Interventions on airways, breathing and circulation including orotracheal intubation or supraglottic device use, use of tourniquets, haemostatic gauzes, pelvic binder, thoracostomies, REBOA or resuscitative thoracotomy and positioning of wide bore vascular access. In case of REBOA a subset of data will be collected (Anatomical zone and duration of balloon inflation). Prehospital fluids and blood products Total volume of prehospital crystalloid, colloid, units of prehospital packed red blood cells, grams of prehospital fibrinogen, volume of prehospital plasma and use of clotting factors (prothrombin complex concentrate). Other drugs Induction agents, vasopressors, osmotic and hypertonic fluids, electrolytes, tranexamic acid.

Table 2. Hospital Study Variables

Trauma Team Activation	Data regarding the presence and activation of a trauma team. Also whether a prehospital activation of a massive transfusion protocol is performed.
Emergency Department Clinical Examination	Emergency department clinical assessment including airways, breathing and circulation, estimation of bleeding. Neurological assessment (GCS, pupils and sensory-motor deficits) Temperature at admission.
Biochemical Data	First Arterial Blood Gas performed at hospital admission (pH, PaO_2, $PaCO_2$, HCO_3, lactate, base excess, hemoglobin) ROTEM (if available) INR value at admission aPTT value at admission

Emergency Department Interventions	Interventions on airways, breathing and circulation including orotracheal intubation or supraglottic device use, use of tourniquets, haemostatic gauzes, pelvic binder, REBOA or resuscitative thoracotomy and positioning of high flow vascular access. In case of REBOA a subset of data will be collected (Anatomical zone and duration of balloon inflation). Emergency department fluids and blood products Total volume of prehospital crystalloids and colloids, units of prehospital packed red blood cells, grams of prehospital fibrinogen, volume of prehospital plasma.
Emergency Department Diagnostics	eFAST (if performed and findings) X-Ray (if performed and findings) Computed Tomography (if performed and findings, date and time of CT)
Emergency Department Outcomes	Hemodynamic status at disposition from the emergency department (Systolic Blood Pressure, Heart Rate) Lactate and Base Excess at emergency department disposal.
Post-Emergency Department Interventions	The patient pathway following disposition from the emergency department is recorded. Patients might be taken into surgery, angiography, intensive care or die. If taken to surgery or angiography details of the procedure and intraoperative findings are recorded. Eventual intraoperative cardiac arrest and ROSC are recorded.
Scores	Injury Severity Score (ISS) is collected according to international coding standards. Sequential Organ Failure Score (SOFA) at ICU admission SAPS2 at ICU Admission

Intensive Care / High Dependency Unit Admission and discharge	Blood Gasses at ICU/HDU admission Blood Gasses 24 hours from ICU/HDU admission Organ failures within the first 24 hours of hospital admission Type and duration of organ support (mechanical ventilation, tracheostomy, vasopressors, renal replacement) Total number of packed red blood cells during first 24 hours (including prehospital transfusion if applicable) Total volume (ml) of plasma during first 24 hours (including prehospital transfusion if applicable) Total number of platelets pool during first 24 hours (including prehospital transfusion if applicable) Total grams of fibrinogen concentrate during first 24 hours (including prehospital transfusion if applicable) Total volume (ml) of crystalloids and colloids during first 24 hours (including prehospital transfusion if applicable) Further organ failures and surgical interventions at seven days from hospital admission Further organ failures and surgical interventions at thirty days from hospital admission Glasgow Outcome Scale - Extended (GOS-E) thirty days from hospital admission Date, condition and location of hospital discharge Primary cause of death

Data collection and management

Anonymized data will be collected via a web-based secure electronic Case Report Form (eCRF) using the RedCap software (Research Electronic Data Capture, Vanderbilt University, Nashville, Tennessee, USA). The data will be securely stored on the study coordinator's local health authority research server (AUSL Bologna, RedCap license from IRCCS Bellaria, Bologna, Italy). Data will be regularly checked for consistency and completeness by the study coordinator and steering committee. Reminders will be sent to local investigators to correct potential irregularities. All participating centres will join a data transfer agreement to define the terms for data transfer

from the centres to the sponsor. All procedures will comply with the European Union Regulation 2016/279 on data protection.

Study Size

The primary endpoint is to describe the current clinical practice and assess the effectiveness of current practice on patients' 30 days mortality. Major trauma patients experience an overall 20% mortality.[2,9] In order to perform a logistic regression analysis using mortality as the dependent variable, 10 events are needed for each covariate inserted in the model as a rule of thumb. Therefore, a model involving up to 10 covariates will need at least 500 patients.

Plan for Analysis

Patients' characteristics and patterns of lesions will be depicted using descriptive statistics and specific analyses are planned for the primary and secondary objectives. The methodology of analysis is also based on the suggestions from the previous work on Multicenter observational prehospital resuscitation on helicopter study by Holcomb et al. [38,39]

Primary objective

The variation in clinical practice will be described through descriptive statistics.
The exploration of factors influencing 30 days mortality will be performed as follows: patients will be divided into two groups based on 30 days mortality, and the prehospital and trauma-related variables resulting significantly different between the two groups will be tested as covariates in a univariable logistic regression model. Finally, the multivariable model building will be performed through the least angle regression selection (LARS) considering as candidate variables all those variables resulting associated with 30 days mortality with a $p < 0.1$ in the univariable analysis. Standard errors will be adjusted considering single HEMS bases as clusters.

Subsequently, the effect size of single interventions, in particular, the prehospital administration of red blood cells, coagulation products and REBOA will be studied through propensity score adjusted logistic regression models.

Secondary objectives

Factors associated with survival to hospital admission will be estimated with a multivariable logistic regression model building as described for 30 days mortality.

Prehospital eFAST accuracy will be tested against CT scan and/or operating room findings of hemoperitoneum. The occurrence of a positive eFAST will be tested as an independent factor in a Cox proportional hazards regression model considering time to definitive diagnostics (CT scan) or treatment (Operating room access). A propensity score matching will be performed to adjust for the covariates that influence the probability of receiving eFAST in the prehospital setting.

A quantilic regression model will be used to test factors associated with the volume of blood product administration during the first 24 hours after hospital admission.

DISCUSSION

Given that the utility of a TR that includes injured patients across a nationwide trauma system is universally established, we aim to obtain data from a large cohort of trauma patients attended by HEMS. We will provide a detailed description of the patients' characteristics, bleeding trauma patients' management strategies, resource use, system organization and performance and their correlation to clinical outcomes. The differences in the management of bleeding trauma patients nationwide, both prehospital and in-hospital, their treatment and therapeutic strategies together with potential outcome association will also be described.

The results generated from this study will complement other large multicentre studies focusing on bleeding trauma patient practice. In addition, for the first time, we aim to collect large-scale national data on trauma resuscitation from the prehospital HEMS phase to the initial in-hospital management.

Bleeding trauma patients is certainly not a naïve research field, however, the nationwide approach can be considered the main strength and novelty of the study since it allows to explore the clinical practice in geographical regions characterized by very different healthcare organizations.

Concluding, SPITFIRE study protocol provides a timely and unique opportunity to generate high-quality evidence regarding prehospital and in-hospital trauma resuscitation. Evidence that we hope will provide useful information for improving the overall management of the bleeding trauma patient nationally and internationally, moreover, it will provide useful quality improvement data for prehospital helicopter emergency services around the country and lastly, we hope, it will make a significant difference to influencing future research questions and improving patient care.

ETHICS AND DISSEMINATION

Ethics

The study has been approved by the Ethics Committee "Comitato Etico di Area Vasta Emilia Centro" (approval date 22/10/2020). Each participating centre / local Principal Investigator is responsible for obtaining local approval in compliance with the local legislation and rules. The national coordinators will facilitate this process.

Major trauma is unpredictable and often incapacitating and thus immediate prospective informed consent from patients might not be possible. Moreover, in the case patients will retain capacity they will likely need immediate life-saving interventions that cannot be deferred to collect study consent. Consent to participate in the SPITFIRE trial will be sought at the earliest opportunity. Patients or legal representatives will be approached by a local study investigator at a time when they are well and able to receive and process information. All reasonable efforts will be put into place to inform patients or their proxies and to obtain informed consent. In case of patients who die before consent is obtained and with no legal representatives recorded data will be included in the study as per indication of the Italian data protection authority, section on scientific research (section 5.3.2 Provvedimento del Garante n. 146 del 5 Giugno 2019). Patients can be removed from the study, at their own or their legal representative's request, at any time.

The study will be performed according to the Helsinki Declaration and International Conference on Harmonization of Good Clinical Practice.

Registration and Funding

SPITFIRE is registered with clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT04760977)
This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The Article Processing Charge for this publication will be offered by the no-profit Fondazione Franca Capurro of Novara.

Dissemination

The study results will be submitted for publication in peer-reviewed international journals and presented at national and international meetings. Study participants will be sent a summary of the final results, including details of their local study population.

Figure Legend

Figure 1 - Current Study Centers (February 2022). Blood drop represents HEMS bases with blood components availability. The Bolzano icon represents the four Alto Adige provincial bases: Bolzano, Bressanone, Lasa and Pontives.

Collaborators (to be indexed and searchable into PubMed)

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Contributors

MT and LG designed the study (Principal Investigator and co-PI). MT, LC and LG drafted the manuscript; CL, AG, CAM, VC, SC, DL, JH, GS, CC and GG critically revised the work for important intellectual content; LG and DA are responsible for the statistical and methodological aspects of the study. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Competing Interests

Prof Holcomb is a consultant with Cellphire, Hemostatics and Arsenal, is Co-founder, Co-CEO and on the Board of Directors of Decisio Health, on the Board of Directors of QinFlow, Zibrio, and Oxyband and a Co-inventor of the Junctional Emergency Tourniquet Tool. The other authors do not report any competing interest.

Patient Consent

Not Required.

Data Sharing Statement

The SPITFIRE steering committee will consider any request on data sharing, on reasonable requests, and decisions will be made after the primary multi-center manuscript has been published.

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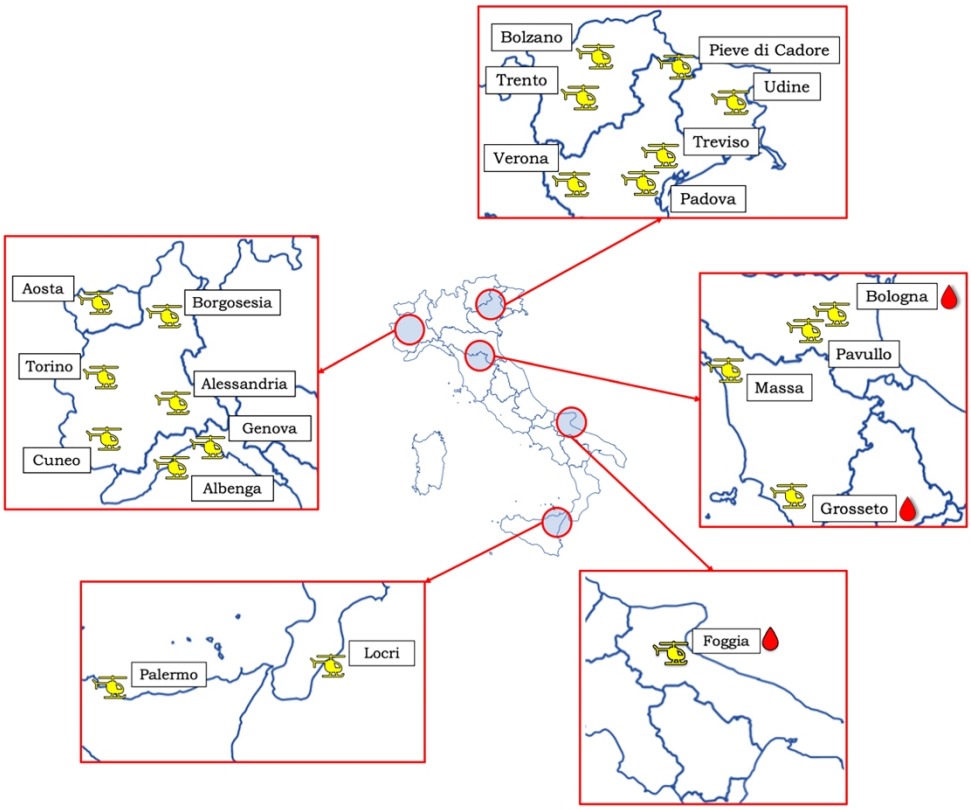

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