Study plan

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Transferability of clinical prediction models for early trauma care

Introduction

Trauma results in millions of deaths annually across the globe, and road traffic injuries are among the top 10 leading causes of death worldwide (1, 2). Each year 9% of the world's deaths are because of trauma, and predictions indicate that this number is likely to increase (3).

Trauma care involves many levels of the health care system. In a typical, high resource setting, the initial management of patients is performed on the scene of the trauma by Emergency Medical Services (EMS). In this prehospital phase; patient data, vital signs and scene information is collected and transferred to the receiving hospital. This information is then evaluated with the help of a system to determine the level of trauma and prepare adequate resources (4). The level of trauma dictates if a full or limited trauma team is activated (5).

Systems to determine the level of trauma can be based on clinical prediction models. Such models are continuously being developed and studied, examining different parameters and different contexts concerning trauma care. These models differ in quality and characteristics, but they generally perform well when predicting survival (6). Many of these models are developed in a single standardized setting such as a large metropolitan area or a major trauma centre but are then supposed to be implemented in different settings, such as non-trauma centres.

What is not fully understood is how this transfer affects the performance of these models. Previous research that studied the transfer of clinical prediction models between settings has

shown that model performance in terms of calibration can be adversely affected (7). However, the aforementioned research studied model transfers between substantially different settings and did not assess more clinically relevant performance measures, such as misclassification.

In trauma, misclassification is often referred to as mistriage. Here, triage refers to the classification of severity as minor or major trauma. Mistriage can be subdivided into overtriage; the incorrect classification of a patient with minor trauma as major trauma, or undertriage; the incorrect classification of a patient with major trauma as minor trauma. Both are detrimental in terms of patient care and distribution of resources.

Thus, the effect of model transfers between contexts within the setting of a single health care system, as well as the effect of such transfers on mistriage have not been studied and represent substantial knowledge gaps. Therefore, the aim of this study is to assess how transfers of clinical prediction models for early trauma care between different contexts within a single health system affect mistriage rates.

Materials and Methods

Study design

We will conduct a registry-based cohort study. Sweden has a nationally encompassing register for registering trauma called SweTrau. We will use SweTrau data to create a clinical prediction model, which we will then transfer between different contexts to study the effects on mistriage.

Setting

In Sweden, trauma is the most common cause of death before 44 years of age. It is estimated that up to 10% of all major trauma patients suffer some form of disability. The societal effects of trauma are also substantial; with the loss of work days comparable to those lost from cardiovascular and malignant diseases combined (8).

The trauma care organization in Sweden is usually clearly defined in major metropolitan areas (albeit the specific routines differ), and trauma patients are transported directly to a predesignated hospital with specific trauma competency and capacity. However, in large, more rural parts of the country, trauma patients are instead transported to the nearest hospital

for stabilization. Once stabilized, they may then be transported to hospitals with more advanced trauma care capacity (9). Most hospitals in Sweden use some form of system to categorize the level of trauma and necessary response. These systems are usually based on the patient's vital signs and injury mechanism, as reported by the EMS before patient arrival, or as registered in the emergency department if the patient arrives by other means (10).

We will use data from SweTrau between 2011 and 2016. Today 95,5% (52 of 55) of Swedish hospitals record trauma cases in SweTrau. Currently the registry includes 55 000 cases, and the board encourages its use in both academic research and more local quality improvement initiatives (11). Included hospitals are both university and non-university hospitals, all of which receive trauma patients.

Patient data is recorded upon arrival to the hospital. All hospital personnel can perform patient registration, but it is recommended they received Abbreviated Injury Scale (AIS) training. The SweTrau inclusion criteria are: Traumatic event with subsequent activation of hospital trauma protocol, admitted patients with NISS (New Injury Severity Score) > 15 and patients transferred to the hospital within 7 days of traumatic event with NISS > 15. SweTrau excludes patients if the only traumatic event is chronic subdural hematoma or if hospital trauma protocol is activated without traumatic event (12).

Recorded variables are registered as prehospital or hospital. Prehospital variables include: types of transport, GCS, SBP, RR, cardiac arrest, prehospital airway management, type of airway management and level of prehospital competency. Hospital variables include: local trauma protocols, type/level of trauma protocol activated, reprioritization of trauma protocol, GCS on arrival, SBP, RR, main type of injury (blunt or penetrating), ASA, mechanism of injury, intention of injury (accident, self-harm or assault), vital initial treatment, base excess, PK/INR, in-hospital airway management, type of airway management, recorded time to normal base excess, time recorded to CT-scan, time recorded to vital initial treatment. The injury is then detailed using AIS-coding which assigns injuries to specific organs and extremities. Lastly follow up is registered with survival 30 days after the traumatic event, Glasgow Outcome Scale at discharge, days in ventilator, date of discharge, highest level of care received, discharged location, transfer to other hospital, autopsy performed (12).

Participants

The eligibility criteria are patients registered in SweTrau, and age 15 or above. This age was decided as the study aims to study adult trauma and not paediatric trauma which differs in physiology, triage and initial care (13). We recognize this age cut-off is not completely without controversy. However, in Sweden patients age ≥15 go to the adult emergency rooms. Also, several guidelines and protocols listed in ATLS (Advanced Trauma Life Support) use age ≥15 as cut-off (4). Patient age will be obtained from the SweTrau register.

Variables

Model Predictors

Our clinical prediction models will include the predictors systolic blood pressure (SBP), respiratory rate (RR) and Glasgow Coma Scale (GCS) on arrival to hospital. The rationale for including these three predictors is that they are part of many established clinical prediction models for early trauma care, such as the Revised Trauma Score (14).

Model outcome

The outcome that will be used to develop the clinical prediction models is all cause mortality within 30 days of the trauma.

Participant characteristics

To describe the patient cohort we will report age, sex, American Society of Anaesthesiologists physical status classification system (ASA), Injury Severity Score (ISS) and New ISS (NISS).

Study outcome

We will use ISS > 15 as the gold standard to define trauma severity as major trauma, and hence patients with ISS ≤ 15 will be considered minor trauma (15). We define overtriage as the event when a clinical prediction model classifies a patient with ISS ≤ 15 as major trauma, and undertriage as the event when a clinical prediction model classifies a patient with ISS > 15 as minor trauma. Clinically, in the event of overtriage, a full trauma team is activated and tasked with the care of a minimally injured patient. The opposite is true with undertriage, where a patient with serious injuries is managed with (potentially) inadequate resources (5). We define the overtriage rate as the number of overtriaged patients divided by all patients. We define the undertriage rate as the number of undertriaged patients divided by all patients. The mistriage rate is defined as the sum of the over- and undertriage rates.

Data sources and measurements

Model predictors, outcome, participant characteristics and study outcome as outlined above will all be obtained from the SweTrau registry. The method of measurement for the model predictors is not specified (for example, if SBP is measured using an automated cuff or manually) in the registry entries. However, in Swedish emergency rooms, patient parameters are usually obtained by a registered nurse or assistant nurse and are assumed to be accurate. Whether the patient is dead or alive 30 days after trauma is manually entered into the registry locally, by each respective hospital. Foreign citizens discharged within 30 days are registered as survivors. Participant characteristics; sex and age are obtained from the patient file before being registered in SweTrau. ASA, NISS and ISS are calculated by hospital personal based on the patient's injuries, and registered.

Bias

Data analysis will be conducted in a step-by-step fashion for each data set, and according to a prearranged analysis plan. The analysis plan is finalised using simulated data. These efforts will be taken to avoid confirmation bias when conducting the data analysis. The analysis plan will be reviewed by an experienced statistician and programmer prior to implementation to ensure objectivity. Neither outcome nor variable will be blinded when conducting data analysis, which will make a structured objective approach even more important.

Study size

All patients matching eligibility criteria listed above. Four data sets will be used to study the transfer of clinical prediction models, each data set representing a different setting. Data set, and sample size considerations are outlined below.

Quantitative variables

SBP and RR will be modelled using restricted cubic splines with four knots placed at equally spaced percentiles and GCS as a continuous linear term. When describing the participant characteristics all quantitative variables will be presented as continuous. ISS will also be presented as dichotomous using ISS > 15 as the cutoff.

Statistical methods

Data sets

The complete SweTrau cohort will be split into four sets of data. High and low volume centres, metropolitan and non-metropolitan centres, multi and single centre data and individual centres.

High and low volume centres

Based on number of patients, two samples will be derived from this data set. High volume centres will be those with in the top quartile of number of patients received. The rest will be low volume centres.

Metropolitan and non-metropolitan centres

This data set will also be split into two samples. The metropolitan sample will consist of greater Stockholm, greater Gothenburg and greater Malmö, as defined by statistics Sweden. The other sample will be patients from non-metropolitan areas.

Multi and single centre data

In this data set multiple samples will be created. Each centre with large enough sample size to develop and validate a model will be their own sample. The multi-centre sample will consist of the combined data from all single centre samples.

Individual centres

This data set will also be split into multiple samples. Each centre with large enough sample size to develop and validate a model will constitute its own sample.

Development sample and validation sample

Each set of data will include at least two samples. The samples will then be split into two subsamples using a temporal split based on the date of traumatic event. The earlier subsample will be the development sample, and the later subsample the validation sample. The development sample will contain 70 events (events being patients who died within 30 days of the trauma) and all non-events (non-events being patient survival 30 days past the trauma) during the same time. The rationale for including 70 events is that we need at least 10 events per free parameter in the logistic regression to obtain stable coefficient estimates (16). The validation sample will contain 100 events and at least 100 non-events (17). See figure 1 for

example using the high- and low volume centre data set, with high volume centres being those in the top quartile of number of patients registered.

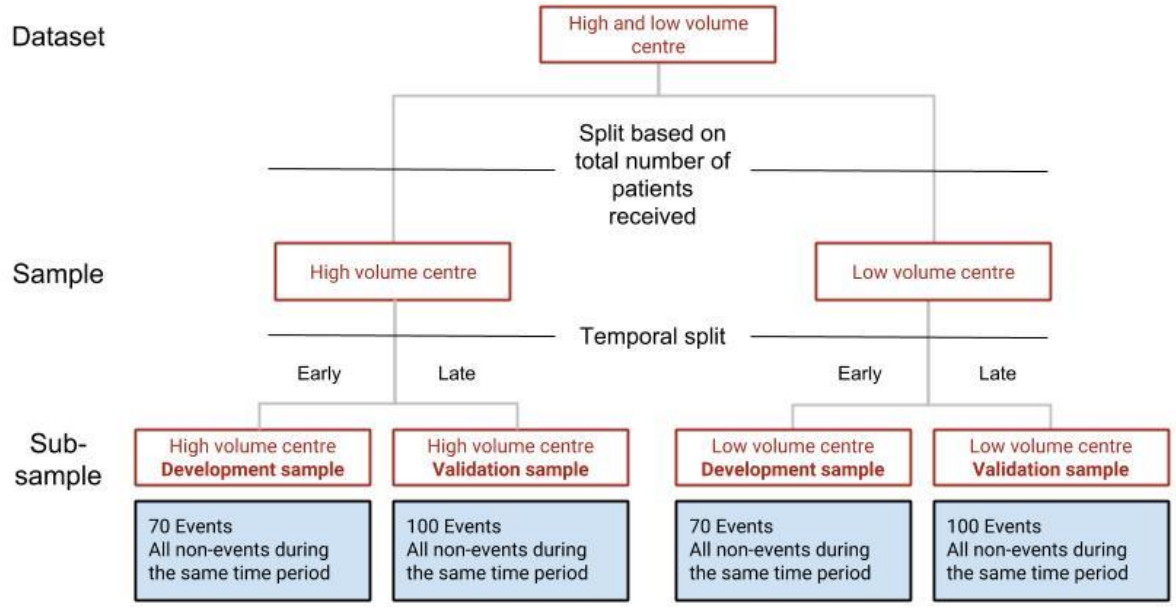

Figure 1: High- and low volume centre data set. Initial split based on number of patients. Temporal split made using date of traumatic event.

The total number of events and non-events per data set will therefore be at least 680. The minimum sample size of development and validation samples will be 140 and 200 respectively. We will perform analyses only on data sets for which all samples include at least the minimum number of patients.

Sequence of analysis

The programming language R will be used for all analyses (18). We will perform the analyses in the sequence of model development, model validation and finally model comparison. These steps will be repeated in each data set. Below we use the transfer of a model from a high-volume sample to a low volume sample as an example to describe the complete procedure.

Model development

In the model development step a clinical prediction model will be developed in the high-volume centre development sample. The model will be developed using logistic regression as implemented in the R function glm. The dependent variable will be all cause mortality within 30 days of trauma and independent variables will be SBP, RR, and GCS modelled as previously described. To avoid overfitting the model we will use a bootstrap procedure to

estimate a linear shrinkage factor that we will apply to the model coefficients (19). The shrunk model will then be used to estimate the probability of all cause 30-day mortality in the development sample. We will then do a gridsearch across estimated probabilities in the development sample to identify the cut-off that optimises overtriage keeping undertriage at less than 5% (20). This cut-off will then be used to classify patients as major or minor trauma.

Model validation

In the model validation step, the model performance will be assessed in the high-volume centre validation sample and in the low volume centre validation data. First the model will be used to estimate the probability of all cause 30-day mortality in each sample. Then the probability cutoff identified in the development sample will be applied to the validation samples, patients will be classified as major or minor trauma, and model performance is estimated.

Model comparison

Finally, in the model comparison step, the difference in model performance between the high and low volume centre validation samples will be calculated. We will use an empirical bootstrap to estimate 95% confidence intervals (CI) around performance and differences in performance estimates. Both bootstrap procedures used will use 1000 bootstrap samples drawn with replacement of the same size as the original samples. The three steps of model development, model validation, and model comparison will be repeated in all four sets of data.

Performance measures

Model performance will be assessed in terms of over-, under-, and mistriage rates as defined above.

Missing data

We will use multiple imputation using chained equations, as implemented in the R package mice, to handle missing data (21). The number of imputations to be created for each data set will be equal to the percentage of missing data in that data set. Quantitative variables will be imputed using predictive mean matching and qualitative variables will be imputed using logistic regression. SBP and RR will be transformed as restricted cubic splines before imputation and imputed as just another variable. All analyses outlined above will then

conducted separately in each imputed dataset. We will present the combined results as the median point estimate along with the minimum value of the lower and maximum value of the upper 95% CI bounds across imputations. This combined CI will henceforth be referred to as CI_{MI}.

Ethical considerations

This study will be conducted in accordance with the four major principles of medical ethics and The Declaration of Helsinki (22, 23).

Respect for autonomy

The respect for autonomy is upheld as Swedish Privacy Law requires the informed consent of all participants. Patients included in SweTrau receive letters detailing that data obtained may be used for scientific purposes. They are also informed that participation is voluntary and that they may withdraw at any time.

The Principle of Beneficence

Throughout the entire study we will attempt to act in the best interest of the patients. In the long run we hope this research will improve the care of trauma patients, and therefore prove beneficial to those affected. We also believe that the patients who consented to research want to contribute to this improvement of care, and as thus by performing this study we hope to honour their wishes.

The Principle of Nonmaleficence

All attempts will be made to not harm any patients included in this study, either intentionally or unintentionally. Data leakage and patient identification constitutes the primary risk. All data obtain will be depersonalized and handled with care to minimize risk of unauthorised access and subsequent patient identification. By implementing these actions, we determine that the risk to the patient population is minimal.

The Principle of Justice

As this study contains no intervention, the principle of justice does not truly apply. However, all cases included from the registry will be treated as equal. It is also our wish that any scientific gains this study may contribute will be implemented in a fair and equal fashion.

Ethical permit

This study is approved by the regional ethics review board in Stockholm, Sweden. Ethical review numbers are 2015/426-31 and 2016/461-32.

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