

## **Efficacy of a tool to predict short-term mortality in older people presenting at emergency departments**

### **Protocol for a multi-centre cohort study**

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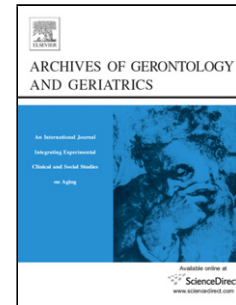
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**Efficacy of a tool to predict short-term mortality in older people presenting at emergency departments: Protocol for a multi-centre cohort study**

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## HIGHLIGHTS

- The CriSTAL checklist is an objective and practical tool to predict short-term death

- Validation in emergency department aims to reduce clinicians' prognostic uncertainty
- The ultimate goal is to encourage timely end-of-life conversations

## ABSTRACT

### Background

Prognostic uncertainty inhibits clinicians from initiating timely end-of-life discussions and advance care planning. This study evaluates the efficacy of the CriSTAL (**C**riteria for **S**creening and **T**riaging to **A**ppropriate **a**lternative care) checklist in emergency departments.

### Methods

Prospective cohort study of patients aged  $\geq 65$  years with any diagnosis admitted via emergency departments in ten hospitals in Australia, Denmark and Ireland. Electronic and paper clinical records will be used to extract risk factors such as nursing home residency, physiological deterioration warranting a rapid response call, personal history of active chronic disease, history of hospitalisations or intensive care unit admission in the past year, evidence of proteinuria or ECG abnormalities, and evidence of frailty to be concurrently measured with Fried Score and Clinical Frailty Scale. Patients or their informal caregivers will be contacted by telephone around three months after initial assessment to ascertain survival, self-reported health, post-discharge frailty and health service utilisation since discharge. Logistic regression and bootstrapping techniques and AUROC curves will be used to test the predictive accuracy of CriSTAL for death within 90 days of admission and in-hospital death.

### Discussion

The CriSTAL checklist is an objective and practical tool for use in emergency departments among older patients to determine individual probability of death in the short-term. Its validation in this cohort is expected to reduce clinicians' prognostic uncertainty on the time to patients' death and encourage timely end-of-life conversations to support clinical decisions with older frail patients and their families about their imminent or future care choices.

**Keywords:** mortality, uncertainty, clinical decision support, validation studies, emergency departments, aged, cohort studies, risk prediction.

### Strengths and limitations of this study

- This cohort study is the largest validation of the CriSTAL tool based on objective parameters available at the point of care
- It is anticipated that prediction of individual risk of death will improve prognostic certainty across health systems
- Follow-up is limited to three months post assessment

### Background

Uncertainty of the time to death in frail older patients on admission to hospital can be challenging in acute settings <sup>1</sup>, and can inhibit doctors from discussing prognosis with elderly patients with a short life expectancy <sup>2</sup>.

Recognition of the *dying* status varies with clinical judgment <sup>3, 4</sup>, the extent of decline and its time course <sup>5</sup>, and the obvious presence of imminent death <sup>6</sup>. Some illness trajectories manifesting as progressive decline with intermittent exacerbations indicate well that end-of-life is inevitable regardless of the time to death <sup>5</sup>. During the last few months of the older patient's life there is an increased use of emergency departments (ED) and in-hospital services <sup>7, 8</sup>. Despite terminal illness, many older patients receive aggressive treatments which may be potentially futile or harmful <sup>9, 10</sup>. Many deaths will be recognized as imminent only in the last few days of life as the clinical picture becomes obvious <sup>11, 12</sup>.

Failure to discuss prognosis and risk of death can compromise appropriate patient care, delays important knowledge being conveyed to patients and their caregivers about their health, and denies personalized end-of-life treatment options including whether to shift from aggressive interventions to supportive care <sup>12, 13</sup>. At times, the prognosis is known or presumed but is not communicated to families even if they want to know and accept that the exact prediction may be uncertain <sup>14</sup>.

Calls for better prognostication models have been made to reduce clinical uncertainty<sup>15</sup> and to better predict short-term mortality<sup>16</sup>, as existing risk stratification instruments for older people in ED do not accurately differentiate risk levels<sup>17</sup> or are reliant on blood tests or do not report calibration or external validation<sup>18</sup>. We previously developed a screening tool: **Criteria for Screening and Triaging to Appropriate aLternative care (CriSTAL)**<sup>19</sup>, based on age, nursing home residency, history of ICU or hospital admission, chronic conditions, and frailty as measured by the Fried Score<sup>20</sup> (Additional file 1). The tool has been tested retrospectively in single centres in Australia and USA among patients receiving rapid response calls after they deteriorated in hospital, indicating good correlation with the outcome of death<sup>21, 22</sup>. The present study is a validation of CriSTAL using a prospective cohort study design in routine ED care in three countries with different health systems to determine its usefulness in supporting end-of-life discussions.

### **Study hypothesis**

The use of an objective list of clinical parameters that can be readily obtained at the point of care can identify older patients at risk of death in the ensuing three months to better predict this event and enhance prognostic certainty near the end of life.

### **Objectives**

1. To establish the efficacy of individual and combined parameters in the CriSTAL tool to predict In-hospital death or post-discharge death up to 3-months post admission.
2. To determine the minimum number of variables sufficient to adequately predict in-hospital or post-discharge death.

### **Methods**

The CriSTAL validation study is a prospective observational project to determine how accurately the CriSTAL tool can anticipate death for older people at high risk.

### **Setting**

This study will be led by academics and clinicians in these different healthcare systems: Sydney (Australia) in collaboration with clinicians from EDs in Odense, Bispebjerg, Esbjerg, Copenhagen (Denmark) and Cork (Ireland).

### **Participants**

Consecutive patients aged 65 years and above with any diagnosis presenting at ED in five Australian teaching hospitals, four Danish hospitals and one Irish hospital are eligible for study participation if admission is authorised for at least one day and written consent (or surrogate



consent for those unable to independently provide written consent) is obtained to participate, respond to follow-up telephone contact around three months post discharge, and allow access to data for the follow-up period. All participants will be assigned a unique study identifier for the purpose of follow-up.

### **Exclusion criteria**

Patients discharged from emergency departments before enrolment; patients and/or surrogates unable to communicate in the local language (English or Danish); and cognitive impairment or dementia, or a decreased level of consciousness, unless there is a consenting surrogate to become the informant authorised to provide the patients' information.

### **Procedure**

Eligible subjects will be identified and recruited in the Emergency Department of each participating hospital by registered nurses with experience in emergency, aged care or intensive care or junior medical officers. To minimise bias, these interviewers are purpose-trained for protocol adherence, standard administration of CriSTAL, conduct of targeted searches in the electronic health record, data entry and quality assurance activities. Enrolment and baseline data collection including demographics and clinical items will take place for all eligible patients present during weekday business hours only (See process in Figure 1). Data items not found in the clinical records will be investigated by asking the patient or accompanying relative. Reasons for non-participation will be documented as well as circumstances of loss to follow-up.

Frailty will be ascertained using the Fried frailty phenotype<sup>20</sup> consisting of five parameters added for a score of 0 to 5: self-reported exhaustion; unintentional or unexplained weight loss of 10lbs in the past year; slow walking speed (4.5 meters in >7 seconds); weakness defined as low grip strength for writing or handling small objects, difficulty or inability to lift heavy objects  $\geq 4.5\text{Kg}$ ; and inability for physical activity or new inability to stand. For cross-comparison, we will measure frailty concurrently using the Clinical Frailty Score<sup>23</sup> which is a pictorial scale supplemented with brief questions on activities of daily living to estimate the score from 1 (very fit) to 9 (terminally frail). All frailty instruments will refer to the patient's physical functioning and weakness the week before admission, that is, their usual state before the acute reason for presentation in emergency. We will use this as a marker of chronic frailty or robustness. Disability due to stroke is also documented on admission as part of the CriSTAL tool.

A CriSTAL score will be estimated by assigning one point to each of the items on the checklist, and could range between 2 and 32. Hospital discharge outcomes will be checked weekly from the hospital electronic databases by recruiting nurses. Post-discharge follow-up, using a standard questionnaire (Additional file 2), will take place around 3 months after admission via direct

telephone contact with participants or their nominated surrogate.

### **Missing data**

All efforts will be made to document each item including search in electronic and paper records, and asking the patient or surrogate informant. If an item is not mentioned or there is no evidence of it in the record, it will be assumed as negative, e.g. no evidence of proteinuria= no proteinuria.

### **Loss to follow-up**

Up to five attempts to contact participants will be made at different times and days of the week before declaring them lost to follow-up. Clinical and demographic items are to be obtained from the electronic records and if not available, verbally from patients or their surrogates. While paper forms will be used at each stage for subsequent quality assurance, all recruitment and follow-up data will be entered onto a web-based interface with encrypted transferred for storage in a secure university server for data cleaning and analysis.

### **End of study**

The study will end when the last participant has completed 3-month telephone follow-up.

### **Sample size**

As there is no precedent for this testing, the sample for this prospective study is based on pragmatic criteria of multi-centre participation contributing at least 300 eligible study subjects each. All in-hospital deaths will be determined as part of routine documentation, and we assume that 10% would be lost to follow-up and will have incomplete ascertainment of post-discharge death, so over-recruitment will take place –when feasible– to cater for this possible loss.

### **Outcomes**

The primary outcome is death within 3-months and CriSTAL's predictive ability: sensitivity, specificity, positive predictive value, negative predictive value, and Area Under the Receiver Operating Characteristics (AUROC curve). Corresponding values for in-hospital death are secondary outcomes.

### **Statistical Analysis**

Descriptive statistics will be used to present the participants' socio-demographic and clinical profile including chronic comorbidities and frailty, mean CriSTAL scores, follow-up time, and differentials between decedents and survivors. Bivariate analysis of the associations between predictors and the primary outcome will determine whether there are sufficient numbers to include in the initial model. Logistic regression will be conducted to assess predictors of the primary outcome of death within 3 months, and separately the predictors of in-hospital death. The effects of predictors will be

expressed as odds ratios (OR). Likelihood ratio tests will be used to assess the statistical significance of model predictors. Univariable models of all CriSTAL items will be assessed initially. The predictor selection will be based both on statistical grounds and clinical plausibility<sup>19</sup>. All variables with frequencies  $\geq 10$  and with  $p < 0.20$  will be included in a multivariable model and backwards elimination will be used to sequentially remove non-significant items from the model until all remaining variables have a likelihood ratio p-value  $< 0.05$ , except for age and male gender, which will always remain in the model due to and well-recognised frailty gender differentials and associations with mortality.<sup>22, 24</sup> Our clinical prediction model will use backward elimination techniques followed conventional approaches<sup>25</sup>. Continuous predictors will be modelled initially as linear associations. Age will be retained as a continuous predictor and its linearity assessed in the final model. Given the low prevalence of some clinical items among some sub-populations, categories with infrequent items may be collapsed if clinically meaningful (e.g. cerebrovascular disease, chronic heart failure and myocardial infarction into cardiovascular disease; and chronic kidney disease, oliguria and proteinuria may be aggregated as kidney disease).

The final multivariable model's internal validity will be tested using 10,000 random bootstrap resamples to obtain confidence intervals that reflect sampling variability. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CriSTAL for short-term (within 90 days of admission) death from any cause will be estimated as evidence of the predictive performance. We will use ROC curves and the area under the ROC curve (AUROC), also known as the concordance (c) statistic, to investigate the discriminative ability of the model. The 95% confidence intervals for the AUROC of the final multivariable models will be based on percentiles from the bootstrap samples. Assessment of the clinical usefulness of the model used cut-off points to classify patients at various levels of risk. Generalisability will be demonstrated by applying the Australian model (testing cohort) to the European data (validation cohort). The predictive accuracy of CriSTAL at both time points (hospital discharge and at 3 months) will be compared with other existing clinical prediction tools. The sensitivity, specificity and PPV/NPV will be presented from predicted probabilities of 5% to 75%. A decision-curve analysis was produced to guide clinicians on the most appropriate risk thresholds to initiate the end-of-life discussion, as some clinicians may prefer to hold these discussions earlier for greater benefit in terms of awareness, while others might prefer to wait until later when there is higher level of certainty. All data will be analysed using SAS, version 9.4.

### **Data storage and security**

Participants will be identified by a unique Study ID number on all paper or electronic forms to preserve confidentiality. The linkage key will be held by only one assigned data collector at each site under password protection. Baseline and follow-up data will be entered via a web-based interface and encrypted for transmission to the coordinating centre's secure server. Discharge

outcomes will be transferred with password protection to the coordinating investigators. All files will be stored in a secure location at the Simpson Centre for Health Services Research, The University of New South Wales, where the principal investigators are based. Hard copies of data collection forms will remain at the participating institutions in Europe but will be gathered by the coordinating centre for Australian hospitals. Data will be safely deleted and hard copies destroyed 7 years after initial collection as per Australian practice.

### **Ethical considerations**

Any patient or surrogate who wishes to withdraw can do so at any time by telephone or letter, or completing the form offered on recruitment. Reasons will be documented.

People responding to follow-up telephone calls may experience distress if the participant has died since enrolment or if the participants themselves are lonely or depressed following hospital discharge. Staff following up participants by telephone are experienced at dealing with end-of-life issues and will provide emotional support and referral to relevant local support services if required.

### **Discussion**

The aim of the present study is to test whether a screening tool to estimate risk of death at the point of care could be embedded in routine care using easily collected information for clinicians admitting patients in the ED.

This multicentre prospective study will use the CriSTAL checklist <sup>19</sup> as a screening instrument for use in ED to predict death in-hospital and in the short term. Comparisons of performance as clinical predictor with individual parameters in the model as well as a summary score will be undertaken. The CriSTAL tool may be used as the basis for referring older patients with life-limiting illness for palliative care services or community-based terminal care.

CriSTAL's discriminant power will be compared with other published mortality predictors.

Recommendations for future use across countries will likely include caveats about results reflecting differences in admission policies, clinical practices and casemix across the three diverse health systems..

### **Limitations**

For some of the chronic conditions small numbers of subjects may result in limited opportunity to test the predictability of those individual parameters, so composite risk factors by organ or system will be estimated to prevent underestimation of the association. While, we acknowledge that aggregation of conditions makes the untangling of individual effects infeasible, this statistical approach can flag potential predictors by organ or system for future reference. Data for those with tentative diagnostic criteria on admission will be assumed as not present, as only confirmed diagnosis at the point of care can be included as predictors. This may result in underestimation of the prevalence of chronic disease in the sample and/or reduced study power.

### **Practical implications**

The clinician-driven application of the CriSTAL checklist before admission to hospital in a large sample of older patients presenting at emergency services across ten hospitals in three countries is indicative of the need to reduce prognostic uncertainty near the end of life across health systems.

We anticipate that by this analysis will demonstrate the usefulness (or otherwise) of the CriSTAL clinical prediction tool to improve prognostic certainty at the point of care. This knowledge will assist in flagging elderly frail patients at risk of short-term death who might be eligible for an end-of-life discussion involving their caregivers and including more informed choices. If these options are aligned with their preferences such as community-based care and less invasive care pathways the discussion has the potential to minimise unnecessary suffering and potentially use scarce health system resources more cost-effectively.

### **Dissemination**

Data will be aggregated and anonymised, so no images or individuals will be identifiable. The datasets generated and analysed in the course of this study will not be shared outside the participating institutions as a requirement of the ethics committee. However, materials may be shared, i.e. database structures, screening tool, recruitment manual, and all results will be presented in the body of the text and supplementary information files. It is anticipated that study results will be submitted for presentation at the European Association of Palliative Care Congress in 2018, the Australasian College of Emergency Medicine annual scientific meeting 2018, and the National Health Round Table on Health Improvement 2019 in Australia. We also have extensive policy and practice networks where the results and implications for routine care will be presented and adoption into clinical practice will be encouraged if the results show benefit.

### **Authors' contributions**

MCM designed the study protocol with contributions from EL, RMT and KH. MCM produced all study materials and EL led the data collection across all hospitals in Australia with assistance from MP at one site. MCM conducted the univariate and logistic regression analyses, and RMT led the bootstrapping analyses and production of the algorithm. HA and SM coordinated the recruitment of emergency departments in Australia and contributed to the practicalities of the design and promotion of the project in the clinical networks. HA retrieved and interpreted Triage categories. BGL contributed to the conceptualization of the validation analysis and data interpretation. SA, JM, SS, MP, AH, LW, MB, DB, JAP, BNJ, and JBM contributed as site coordinators supporting data collection and contributing comments on practicalities. MK, MOS, AE, HN, HS, HN, JJJ, ROJ, and JLP were data collectors for all stages of the project in Europe. CWC designed and maintained the

web-based interface contributing quality control, data integrity and conceptualisation of the algorithm.

### **Funding and role of the funding source**

All participating hospitals committed to making in-kind contributions of staff time to collect data and undertake quality assurance tasks. This work is supported by a grant from the National Health and Medical Research Council of Australia [grant # 1054146]. The funding body has no role in the development of the research question, study design, analysis, interpretation, conclusions of the review, or in the writing of the manuscript or the decision to submit it for publication.

### **Declarations**

#### **Ethics and Consent to Participate**

This multi-centre study received endorsement from the South Eastern Sydney Local Health District Ethics Committee (#15/026 HREC/15/POW/55) for all the Australian sites; the Irish hospital obtained individual institutional approval from Cork University; the Danish hospitals obtained endorsement with a waiver for ethics submission from De Videnskabsetiske Komiteer for Region Syddanmark. Written consent to participate was obtained in person individually from either the patient or their surrogate at every site after the study was explained and the project Information Sheet was given to every participant at all sites.

#### **Competing Interests**

MCM and KH developed the CriSTAL tool and have retrospectively validated it in Australia and the US. All other authors declare that they have no conflict of interest.

#### **Availability of data and materials statement**

Data for this study will be published in table/graphic format and as additional supported files but not available for sharing on repositories given the restrictions of the ethics committee. The two lead authors are available to reply to data queries by email.

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**Figure 1. Face-to-face recruitment and telephone follow-up of eligible older patients**

Legend. ED=Emergency Department. CriSTAL=Criteria for Screening and Triaging to Appropriate Alternative care.



