Pilot Project for a Web-Based Dynamic Nomogram to Predict Survival 1 Year After Hip Fracture Surgery

McLeod, Graeme; Kennedy, Iain; Simpson, Eilidh; Joss, Judith; Goldmann, Katriona

DOI:
10.2196/preprints.34096

Publication date:
2022

A pilot project informing the design of a web-based dynamic nomogram in order to predict survival one year after hip fracture surgery

Graeme McLeod, Iain Kennedy, Eilidh Simpson, Judith Joss, Katriona Goldmann

Submitted to: Interactive Journal of Medical Research
on: October 13, 2021

Table of Contents

A pilot project informing the design of a web-based dynamic nomogram in order to predict survival one year after hip fracture surgery

Graeme McLeod[1*] MBChB, MD, FRCA, FFPMRCA; Iain Kennedy[1*] FRCA; Eilidh Simpson[2] MB ChB; Judith Joss[1*] FRCA, FFICM; Katriona Goldmann[3]

[1]Ninewells Hospital NHS Tayside Dundee GB
[2]Crosshouse Hospital Kilmarnock GB
[3]William Harvey Research Institute Barts and the London School of Medicine & Dentistry London GB
[*]these authors contributed equally

Corresponding Author:
Graeme McLeod MBChB, MD, FRCA, FFPMRCA
Ninewells Hospital
NHS Tayside
Dundee
GB

Abstract

Background: Hip fracture is associated with high mortality. Identification of individual risk informs anesthetic and surgical decision making and can reduce the risk of death. However, interpretation of data, and application of research findings can be difficult, and there is a need to simplify risk indices for clinicians and lay-people alike.

Results
Twenty-four (7.3%) patients died within 30 days, 65 (19.8%) within 120 days and 94 (28.6%) within 365 days of surgery. Independent predictors of mortality common to all models were admission Age, BMI, and creatinine, lactate and their combination.
Age and BMI inversely correlated with mortality. Presentation with a creatinine level of 90 mol.L-1 increased the odds of death OR 2.9 (1.4 - 6.0) 365 days after surgery compared to an admission level of 60 mol. L-1 Presentation with a plasma lactate level of 2 mmol. L-1 increased the odds of death OR 2.2 (1.1 - 4.5) 365 days after surgery compared to a plasma lactate level of 1 mmol. L-1. Patients presenting to hospital with a BMI of 30 kg.m-2 were less likely to die within 365 days OR 0.41 (0.17 - 0.99) after surgery compared to patients with a BMI of 20 kg.m-2.
We presented four models in Shiny. Data entry created Kaplan-Meier graphs and outcome measures (95%CI).
Conclusion
We developed easy to read and interpretable web-based nomograms for prediction of survival after hip fracture surgery.

Objective: Our primary objective was to develop a web-based nomogram for prediction of survival 365 days after fracture hip surgery.

Methods: We collected data from 329 patients up to 365 days after hip fracture surgery and built four models using packages in RStudio. A global Cox Proportional Hazards Model was developed from all covariates. Covariates included sex, age, BMI, white cell count, lactate, creatinine, hemoglobin, C-reactive protein, ASA status, socio-economic status, duration of surgery, total time in the operating room, side of surgery and procedure urgency.
We also developed a Cox proportional hazards model (CPH). a logistic regression model (LRM), and a generalized linear model (GLM) for binomial response data using iterative data reduction and elimination. We wrote an app in Shiny in order to present the models in a user-friendly way. The app consists of a drop-down box for model selection, horizontal sliders for data entry, model summaries, and prediction and survival plots. A slider selects patient follow-up over 365 days.

Results: Twenty-four (7.3%) patients died within 30 days, 65 (19.8%) within 120 days and 94 (28.6%) within 365 days of surgery. Independent predictors of mortality common to all models were admission Age, BMI, and creatinine, lactate and their combination.

Age and BMI inversely correlated with mortality. Presentation with a creatinine level of 90 mol.L-1 increased the odds of death OR 2.9 (1.4 - 6.0) 365 days after surgery compared to an admission level of 60 mol. L-1 Presentation with a plasma lactate level of 2 mmol. L-1 increased the odds of death OR 2.2 (1.1 - 4.5) 365 days after surgery compared to a plasma lactate level of 1 mmol. L-1. Patients presenting to hospital with a BMI of 30 kg.m-2 were less likely to die within 365 days OR 0.41 (0.17 - 0.99) after surgery compared to patients with a BMI of 20 kg.m-2.
We presented four models in Shiny. Data entry created Kaplan-Meier graphs and outcome measures (95%CI).

Conclusions: We developed easy to read and interpretable web-based nomograms for prediction of survival after hip fracture surgery. Clinical Trial: Nil

(JMIR Preprints 13/10/2021:34096)
DOI: https://doi.org/10.2196/preprints.34096

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**
Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.
Only make the preprint title and abstract visible.
No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**
Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v
Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http

Original Manuscript

A pilot project informing the design of a web-based dynamic nomogram in order to predict survival one year after hip fracture surgery

Iain Kennedy,[1] Eilidh Simpson[2], Katriona Goldmann[3], Judith Joss [4], Graeme McLeod. [4 5]

1 Specialty Registrar, 4 Consultant, Department of Anaesthesia, Ninewells Hospital, NHS Tayside, Dundee

2 Clinical Teaching Fellow, Emergency Department, Crosshouse Hospital, Kilmarnock

3 PhD student, Centre for Experimental Medicine & Rheumatology, Queen Mary University of London

5 Honorary Professor, University of Dundee, Dundee, UK.

Correspondence to:

Graeme McLeod

Consultant & Honorary Professor of Anaesthesia

Institute of Academic Anaesthesia

Ninewells Hospital & University of Dundee, UK.

DD1 9SY

Email: g.a.mcleod@dundee.ac.uk

Keywords: hip fractures; anesthesia; surgery, orthopedic; analysis, survival

Twitter: @gamcleod2; @judejoss

Short title: Design of a web-based nomogram

Abstract

Background

Hip fracture is associated with high mortality. Identification of individual risk informs anaesthetic and surgical decision making and can reduce the risk of death. However, interpretation of mathematical models and application to clinical practice can be difficult, and there is a need to simplify risk indices for clinicians and lay-people alike.

Objectives

Our primary objective was to develop a web-based nomogram for prediction of survival up to 365 days after fracture hip surgery.

Methods

We collected data from 329 patients. Our variables included sex, age, BMI, white cell count, lactate, creatinine, hemoglobin, C-reactive protein, ASA status, socio-economic status, duration of surgery, total time in the operating room, side of surgery and procedure urgency. Thereafter, we internally calibrated and validated a Cox Proportional Hazards (CPH) model of survival 365 days after hip fracture surgery, logistic regression models 30-, 120- and 365-days after surgery and a binomial model.

In order to present models on a laptop, tablet or phone in a user-friendly way, we built any app using Shiny (RStudio). The app consisted of a drop-down box for model selection, horizontal sliders for data entry, model summaries, and prediction and survival plots. A slider represents patient follow-up over 365 days.

Results

Twenty-four patients died within 30 days, 65 (19.8%) within 120 days and 94 (28.6%) within 365 days of surgery. For all models, independent predictors of mortality were: age, BMI, creatinine and lactate. The logistic model also incorporated WCC.

For example, using the CPH model, mortality differed as follows: age 80 yr vs 60 yr, HR 0.6 (0.3 to 1.1); plasma lactate levels of 2 $mmol.L^{-1}$ vs 1 $mmol.L^{-1}$, HR 2.4 (1.5 – 3.9); and plasma creatinine levels 60 vs 90 $\mu mol.L^{-1}$, HR 2.3 (1.3 – 3.9).

Conclusions

In conclusion, we provide an easy-to-read web-based nomogram that predicts survival up to 365 days after hip fracture. The CPH and logistic models model showed good discrimination (c-indices 0.732 and 0.781 respectively).

Introduction

Seven out of one hundred patients die in the first 30 days after hip fracture [1-4]. Mortality 365 days after hip fracture surgery varies between 14% and 23% of patients [5, 6]. Identification of individual risk can inform anaesthetic and surgical decision making, and potentially improve outcomes.

However mathematical models can be complex and difficult to interpret. The effect of changes in a continuous or categorical variable may not be obvious. Graphical presentation of data is a pivotal technique in science and key to better communication[7].

Nomograms present covariables in a relatively easy way, and are used commonly to inform clinicians and patients about the risk of mortality in prostate[8] cancer patients.

However, predictive indices are difficult to interpret and apply to individual patients[9]. Apps can translate statistical modelling using R packages (R Studio Version 1.3.1093) into easy-to-understand web-based interactive nomograms (Shiny, RStudio), that readily demonstrate differences between low-risk and high-risk patients.

One example is the DynNom package[7] in R that pre displays the results of statistical models as a dynamic nomogram, and readily allows individual prediction with 95% confidence intervals.

Anaesthetic guidelines and protocols increasingly drive standardization of practice[10]. However, we believe that individual identification of risk is more likely to improve outcomes[11].

Several risk specific and generic surgical risk indices are available that predict mortality after hip fracture surgery, but most are limited to prediction of mortality 30 days after operation. Indices discriminate well, but lack adequate calibration [12]. The Nottingham

Hip Fracture Score has validated nationally [2] and internationally [13] and is commonly used, albeit its 365-day score discriminates only between low and high-risk patients. Moreover, the more complex a statistical model, due to non-linearity and interactions, the more difficult is to comprehend and apply. As such, survival models based on time to death data[14] are uncommon.

Therefore, a need arises to develop an easy to interpret app for time to event as well as binary outcome data. Proving the apps utility locally, would provide the platform for prospective development of a large multicentre database that would inform a statistical model, with high calibration and discrimination, that could be used easily at the bedside using a laptop, tablet or phone in order to inform staff and lay-people of outcome after hip fracture surgery.

Therefore, our primary objective was to develop a web-based nomogram from clinical data collected over an 8-month period from patients undergoing hip fracture surgery in a single tertiary center.

Methods

We conducted a retrospective study of patients undergoing fractured hip surgery. Our study consisted of data collection, statistical modelling and app development.

Data collection

We collected preoperative and operative data from all patients presenting for hip fracture surgery in Ninewells Hospital, Dundee, over an 8-month period between 1st May 2016 and 31st December 2016. Patients were followed up for one year by reviewing case notes, anesthetic charts and operative notes as part of a 4th year medical student project. Caldicott Guardian approval was obtained from the University of Dundee on

16th October 2016. In the UK, Caldicott Guardian approval provides ethical consent for interrogation of anonymous clinical databases.

Data included patient characteristics, comorbidities, and health status. Patient characteristics recorded on admission included: age; sex; body mass index (BMI); side (left or right); type of fracture (intracapsular or extracapsular); pre-fracture residence; and a rank social deprivation score based on 6976 data zones from the Scottish Index of Multiple Deprivation database (SIMD16)[15]. We used the SIMD16 vigintile database that ranks deprivation from 1 (most deprived residential area) to 20 (least deprived residential area)[16]. Blood tests (hemoglobin, white cell count, creatinine, lactate and C-reactive protein (CRP)) were taken on hospital admission. With regard to surgery, we noted the American Society of Anesthesiologists (ASA) status of the patient; type of anesthesia (general or spinal); surgical implant; and time of operation. Operations performed between 0900h and 1700h were classified as “daytime”; between 1700h and 2200h as “evening”; and from 2200h to 0900h as “night-time” procedures. Postoperatively, we noted the need for transfusion; presence of acute kidney injury; cardiovascular complications such as pulmonary embolus or myocardial infarction; and infection from any source (wound, urinary or respiratory). We recorded the date of hospital discharge and destination. Both the residence of the patient pre-fracture and on ward discharge were classified into home or sheltered housing; care home; acute hospital, rehabilitation setting or long-term hospital care.

Our primary outcome was time to death by any cause within 365 days of hip fracture surgery.

Model development

We developed four statistical models: a global Cox proportionality hazards model using all available covariates (global CPH), a Cox proportional hazards model (CPH), a

generalised linear model (GLM) and a logistic regression model (LRM). Models and nomograms were developed using the R packages "shiny", "ggplot2", "ggpubr", "plotly", "stargazer", "rms", "shinythemes" and "plotly" [16].

Our modelling strategy was based on that recommended by Harrell and Steyerberg [15]. We selected variables based on our clinical experience and evidence from published studies. We collected as much pertinent data as possible, with wide distributions for predictor values. We hypothesized that continuous variables were nonlinear. Imputation replaced missing covariables with the median value. We restricted the number of events per variable (EPV) in the model according to the equation EPV = Events or outcomes/15. We prespecified the complexity of the model and allotted 3 cubic splines (knots) to continuous variables initially in order to detect any nonlinear relationships between variables and outcomes, and one degree of freedom to categorical data.

We first created a global model using all variables and tested the association of each predictor with outcome adjusted for all other predictors and the number of degrees of freedom (df) used. We reduced the model by calculating the number of degrees of freedom that could be spent, and decided how they should be spent. We ranked the apparent importance of predictors of death by plotting Akaike's information criterion (AIC) defined as χ^2 - 2 df. Initial estimation of shrinkage (γ) needed used the formula $\gamma = (\chi^2 - p)/\chi^2$). We also interpreted the model graphically and decided which parameters should be retained for bootstrap validation of calibration and discrimination. Continuous variables that showed a linear relationship with outcome were restricted to one degree of freedom.

Overfitting and effects of shrinkage were assessed using the corrected calibration slope. This was obtained using bootstrapping bias-corrected (overfitting - corrected)

estimates of predicted vs. observed values. In order to check proportional hazards assumptions, we examined scaled Schoenfeld residuals.

Model validation

Prediction errors were assessed using the log-likelihood ratio (χ^2) for continuous data and Brier score for binary data. Discrimination the ability to discriminate between low-risk and high-risk patients, used R^2, the g (Gini)-index from 0 to 1, a robust measure of variation, and measures of rank discrimination such as the *c*-index and Somer's D_{xy}. The *c*-index represents the probability of concordance, *c*, between predicted and observed survival, and is equivalent to the Receiver Operator Characteristic (ROC) area under the curve (AUC). Concordance is defined as the proportion of all pairs of subjects whose survival time can be ordered such that the subject with the higher predicted survival is the one who survived longer. D_{xy} is the difference between concordance and discordance probabilities and related to the c-index by the equation $D_{xy} = 2(c - 0.5)$. Internal calibration and validation used the bootstrap.

Model comparisons

Our secondary objectives were to develop a 365-day logistic regression model (LRM) and a 365-day generalized linear model (GLM) for binomial response data for sensitivity analysis, and additional 30-day and 120-day logistic models in order to compare accuracy against the routinely used Nottingham Hip fracture score.

App development

A data scientist (KG) developed an app using Shiny, a package from RStudio that builds interactive web applications with R. We created three files: ui.R to define the user interface A; server.R to interrogate data from the UI, and define the app logic; and

functions.R to combine both and create the Shiny application.

The user interface (iu.R) consisted of a title, side-panel and main-panel. The side-panel contained a drop-down box that contained four models, global CPH, CPH, GLM and LRM; and sliders for input of continuous variables over their range of values, and follow up time (0 – 365 days). The main panel consisted of three tabs: prediction plots; survival plots; and model summaries.

Prediction plots were displayed on a graph with probability on the x-axis. The mean was displayed as a coloured square with horizontal lines representing the 95% confidence interval (CI) for outcome. Survival models showed a Kaplan Meier plot of estimated survival probability over time. The app can be viewed at https://hip-fracture-modelling.shinyapps.io/hip-fracture-modelling/

Statistical analysis

Continuous variables were presented as mean (SD) and analysed using Aspin-Welch Unequal-Variance Test. Non-parametric data was presented as median (IQR [range]) and analyzed using the Mann-Whitney U test. Cross-tabulation of categorical data count (n) was analyzed used χ^2. Measurement of AUROC of the Nottingham Hip fracture score was undertaken using GraphPad Prism 9 (GraphPad, San Diego, CA)

Results

Data collection

We recorded data from 329 patients, of whom 224 (68%) were female and 85 (32%) were male. Four percent of biochemical data were missing, and replaced with the median value. Over two thirds of patients (n = 224 (68%)) were classified as American Society of Anesthesiologists (ASA) category 3 or ASA 4. This is compatible with severe systemic disease (ASA 3) that is a constant threat to life (ASA 4). Twenty-four patients died within 30 days, 65 (19.8%) within 120 days and 94 (28.6%) within 365 days of surgery. Patient characteristics categorised according to survival or death within 365 days are shown in Table 1.

Table 1 Description of variables (n = 329) categorised according to survival or death 365 days after hip fracture surgery.

Variable	***Survived (n = 235)***	***Died (n = 94)***	***Difference (95%CI) Odds Ratio (95%CI)***	***P-value***
Age *(years)*	82.5 (10.0)	80.9 (9.6)	1.5 (0.8 - 3.9)	0.21
Sex *Male:Female (n)*	61:174	24:70	1.0 (0.6 - 1.7)	0.94
BMI *(kg.m^{-2})*	24.2 (5.7)	21.8 (4.2)	2.4 (0.9 - 3.8)	0.002
ASA *I:II:III:IV (n)*	7:62:113:27	0:5:58:26		<00001
Residence (n) *Home: Care home: Rehabilitation: Acute hospital: NHS continuing care:*	189:41:3:1:1	46:45:3:0:0		<0.0001
Deprivation *SIMD20 0 - most deprived to 20 - least deprived*	11 (6 - 16 [1 - 20])	12 (8 - 16 [1 -20])	1.0 (-1.0 - 2.0)	0.42
Stay *(days)*	12.6 (10.2)	12.1 (8.2)	0.5 (-1.7 - 2.6)	0.67
Side *Left: right (n)*	123:112	50:44	1.0 (0.6 – 1.6)	0.89
Implant *Bipolar: CHS: CPT: Thompson's: femoral nail (n)*	18:80:26:88:23	3:35:1:45:10		0.70
Hb *(g.L^{-1})*	120.3 (18.0)	115.6 (15.0)	4.7 (0.8 – 8.6)	0.01
WCC *(10^{9} L^{-1})*	11.8 (6.1)	11.1 (3.2)	0.8 (-0.2 - 1.8)	0.14
CRP *(mg.L^{-1})*	6 (3-25[2-299.0])	13 (3 - 46[3 - 273])	1.0 (0.0 – 3.0)	0.046
Lactate *(mmol.L^{-1})*	1.47 (0.74)	1.70 (0.92)	0.24 (0.0 -0.48)	0.04
Creatinine *(micromol.L^{-1})*	71.1 (27.5)	89.2 (42.0)	18.2 (8.4 - 27.8)	0.0003
Time *Daytime (09:00 – 17:00): Evening (17:00 – 22:00): Night (22:00-09:00) (n)*	196:37:2	78:14:2		0.02
Discharge (n) *Home: Care home: Rehabilitation: Acute hospital: NHS continuing care: Died in hospital*	100:61:54: 15:7:2	13:42:18: 6: 3: 8		<0.0001

Model development

A global Cox proportionality hazards model using all covariates (global CPH), a Cox proportional hazards model (CPH), logistic regression models (LRM) and a generalized linear model (GLM) were constructed from data.

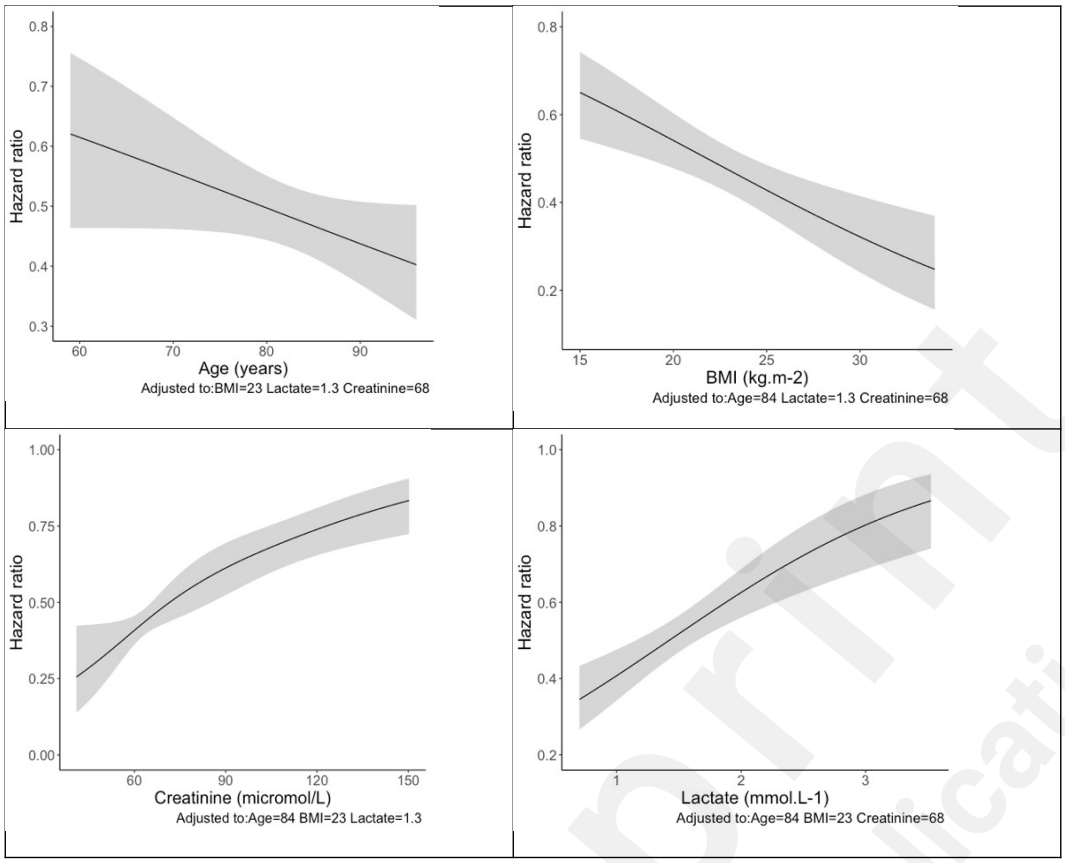
The global CPH model took all covariates into account, whereas the final validated model was built within the statistical constraints discussed in the methods. Graphs in Fig 1 show continuous relationships between covariates and probability of death using the final CPH model. The non-linear relationship between creatinine and risk of death (hazard ratio) was created using cubic splines (Fig 1).

Using the CPH model, independent predictors of mortality were: increased age, BMI, creatinine, lactate and their combination.

Examples of differences in mortality on admission included: age 80 yr vs 60 yr, Hazard Rate (HR) 0.6 (0.3 to 1.1); plasma lactate levels of 2 $mmol.L^{-1}$ vs 1 $mmol.L^{-1}$, HR 2.4 (1.5 – 3.9); and plasma creatinine levels 60 vs 90 $\mu mol.L^{-1}$, HR 2.3 (1.3 – 3.9).

Fig 1. Cox proportionality survival model up to 365 days after hip fracture surgery. Hazard ratios show reduced risk of death with increasing age and reduced BMI. Risk of death rose with increased creatinine and lactate levels. Note the non-linear increase in risk with creatinine, and the increase in risk from values immediately above the

physiological range.



Model validation

Validation results for the global and final CPH models are shown in Table 2.

Table 2. Model validation. Global and final Cox proportional hazards models. Final model developed after Iterative data reduction and calibration using bootstrap. Final model shows good validation using 329 patients. R^2 coefficient of determination; LR (χ^2), likelihood ratio (LR) chi-square test; Dxy, Somer's Dxy test; c-index, Concordance index; g, Gini's index.

	R^2	LR (χ^2)	P-value	Dxy	*c-index*	g
Global CPH 365	0.364	45.328	0.002	0.623	0.812	1.897
Final CPH 365	0.231	43.113	<0.010	0.474	0.732	1.360

Model comparisons

Predictive variables identified using CPH were similar to the predictive variables identified using 365-day logistic regression and 365-day binomial models by CPH (Table 3).

Table 3. Independent variables predicting mortality in CPH, logistic and binomial models 365 days after hip fracture surgery. Variables common to all models included age, BMI, lactate and creatinine. (') = non-linear restricted cubic splines. Regression coefficients (95%CI).

Dependent variable	365-day Final CPH	365-day LRM	365-day Binomial
Age	0.976	-0.023	-0.018
	(0.947 to 1.007)	(-0.062 to 0.016)	(-0.056 to 0.020)
BMI	0.913**	-0.115**	-0.126**
	(0.862 to 0.967)	(-0.199 to -0.032)	(-0.205 to -0.047)
WCC		0.138	-0.028
		(-0.109 to 0.385)	(-0.105 to 0.048)
WCC'		-0.196	
		(-0.453 to 0.062)	
Lactate	0.003**	-5.519*	-0.899
	(<0.001 to 0.199)	(-10.812 to -0.226)	(-0.095 to 1.893)
Creatinine	0.906	-0.072	-0.031**
	(0.817 to 1.005)	(-0.198 to 0.055)	(0.008 to 0.055)
Creatinine'	1.185*	0.133	
	(1.030 to 1.364)	(-0.042 to 0.308)	
Lactate*Creatinine	1.110**	0.098*	-0.007
	(1.037 to 1.189)	(0.013 to 0.183)	(-0.018 to 0.004)
Lactate*Creatinine'	0.865**	-0.134*	
	(0.788 to 0.951)	(-0.250 to -0.018)	
Constant		5.471	0.491
		(-3.329 to 14.270)	(-3.379 to 4.360)

Validation results for our secondary outcomes, the 30, 120 and 365-day logistic regression models are presented in Table 4.

Table 4 Logistic regression validation results

	R^2	$LR (\chi^2)$	P-value	Brier	Dxy	c-index	g
30-day Logistic	0.714	17.390	0.004	0.069	0.541	0.770	1.348
120-day	0.396	21.280	0.002	0.114	0.706	0.853	2.051
Logistic							
365-day	0.277	37.252	<0.01	0.147	0.562	0.781	1.619
Logistic							

Using our data, we calculated the Nottingham hip fracture score AUROC (95%) to be < 0.61 for all time points (Table 5).

Table 5 Diagnostic results using Nottingham hip fracture score. AUROC (95%)

	AUROC (95%CI)		P-value
30 days	0.576	(0.454	–0.215
	0.698)		
120 days	0.606	(0.538	–0.003
	0.674)		
365 days	0.602	(0.526	–0.011
	0.678)		

An example of an easy to interpret dynamic nomogram is presented in Fig 2. Variables are altered using sliders. The digital nomogram is available on-line at at: https://hip-fracture-modelling.shinyapps.io/hip-fracture-modelling/

Fig 2 Dynamic Nomogram. Image (a) shows sliders that are used to enter data for Age standardized to 80 years and WCC = 10 (10^9 .L^{-1}). Four imaginary scenarios presented differing in BMI, creatinine and lactate.

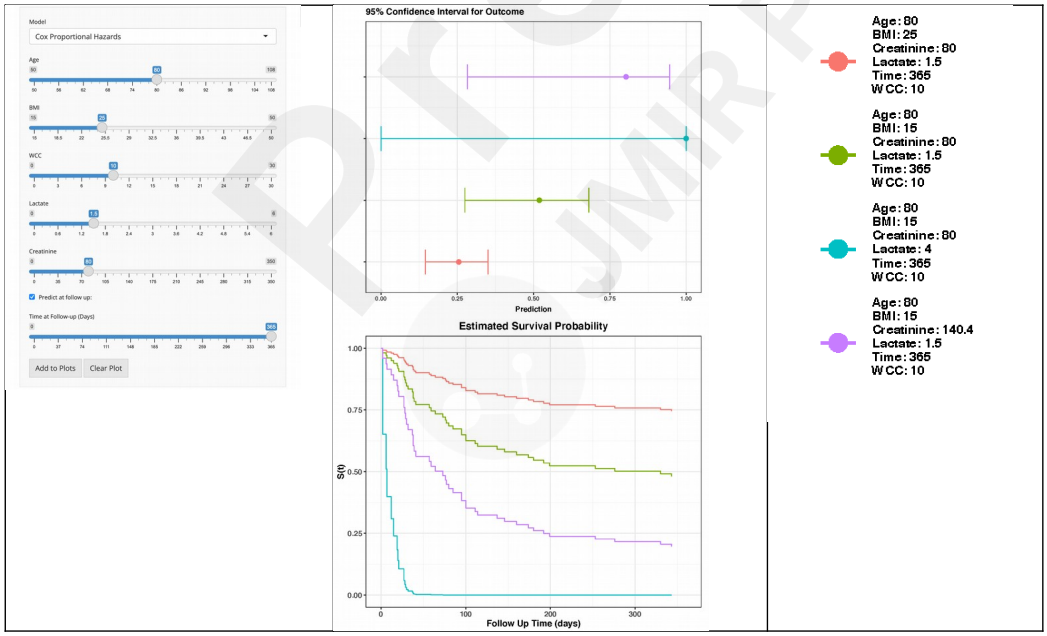
Red line: BMI 25 kg.m^{-2} Creatinine 80μmol.L^{-1} , lactate 1.5 mmol.L^{-1}

Green line: BMI 15 kg.m^{-2} creatinine 80 μmol.L^{-1}, lactate 1.5mmol.L^{-1}

Blue line: BMI 15 kg.m^{-2} creatinine 80 μmol.L^{-1}, lactate 4 mmol.L^{-1}

Purple line: BMI 15 kg.m^{-2} creatinine 140 μmol.L^{-1}, lactate 4 mmol.L^{-1}

Dynamic nomogram available at: https://hip-fracture-modelling.shinyapps.io/hip-fracture-modelling/



Discussion

Principal Findings

We provide proof of concept of a simple dynamic digital nomogram created in R and Shiny that shows individual survival (95%CI) after hip fracture surgery. The nomogram offers an easy, intuitive means of interpreting complicated models. Our models showed good discrimination and calibration. Lactate, creatinine, age and BMI, emerged as important predictors of mortality in all models.

Comparison to Prior Work

Our data are consistent with previous studies demonstrating association between higher serum lactate and mortality following hip fracture [17-19]. For example rise in plasma lactate from 2 $mmol.L^{-1}$ to 3 $mmol.L^{-1}$ increased the hazard ratio by > 25%. Unlike previous studies we did not arbitrarily define raised lactate as levels > 2.5 $mmol.L^{-1}$ [20] or 3.0 $mmol.L^{-1}$[17, 19]. In fact, our non-linear modelling of continuous lactate data showed early steep rises in risk of mortality from 1 $mmol.L^{-1}$. This has implications for clinical practice. It suggests that lower lactate levels than anticipated have an impact on both short- and long-term mortality, and the need for early resuscitation. However, we are not aware of any randomized controlled trials of fluid resuscitation in patients presenting with hip fracture. An association between prolonged lactate clearance and mortality may occur in the surgical ICU population [21], but this cannot be extrapolated to the management of elderly patients with hip fracture. Non-linear modelling of creatinine data also showed early steep rises in risk of mortality. For example, a rise in plasma creatinine from 60 $micromol.L^{-1}$ to 90 $micromol.L^{-1}$ more than doubled the risk of death. Once more this demonstrates that changes just out with the physiological range may impact profoundly on outcome, and that clinicians should be take note of such change, rather than wait for grossly deranged blood results.

Our models also revealed the inverse association of outcome with BMI [22, 23], and that frailty and muscle mass have a significant long-term negative impact on survival after hip fracture surgery. For example, reduction in BMI from 25 $kg.m^{-2}$ to 20 $kg.m^{-2}$ increased the hazard ratio by approximately one third.

Unlike other studies, we failed to show a significant effect of anemia. This probably reflects changes in patient blood management strategies since initial studies into this association [2,3] were published.

We surprisingly showed an inverse relationship between age and outcome, in contrast to many other models[12, 24, 25]. This reflects the increased comorbidities in our younger population and therefore, limits the applicability of our model to other populations.

Nevertheless, for comparison, we applied the Nottingham hip fracture score to our data. Surprisingly, the Nottingham score showed much poorer discrimination compared to our dataset with AUROC values < 0.61 and lack of significance for 30-day prediction of mortality.

Strengths and Limitations

First, rather than just focus on 30-day mortality, we followed our patients for 12 months in order to obtain a detailed, temporal overview of outcomes after hip fracture surgery. Most models, in contrast, focus on measurement of 30-day mortality [4,7,9,10,11,12], and tend to reflect events during hospital stay. For example, the Nottingham Hip Fracture Score also predicts 1-year mortality [13], but divides patients according to a binary “low risk/high risk” classification based on a cut-off score.

Second, we used modelling techniques available on R. Non-linearity of creatinine and interaction with lactate justified our application of restricted cubic splines to continuous data. Although this allocated three degrees of freedom to continuous variables, this

technique improved the accuracy of the model. We used bootstrapping to validate our model. The advantage of bootstrapping is that the entire dataset can be used, unlike data-splitting which reduces the sample size for both model development and testing. Variable selection or stopping rules were not used: these methods provide regression coefficients that are too high and confidence intervals that are too small. Neural networks such as support vector machine, naive Bayes classifier and random forest classifier have been applied to hip fracture datasets but were no better than logistic regression in predicting outcome after surgery[26].

Third, our mortality was in-line with national data. Mortality increased from 7.3% at 30 days to 28.6% at 365 and allowed us to incorporate five variables with good calibration and validation.

However, fourth, we had insufficient data to generate a model that incorporated all potential confounders. We suggest investigators capture data from the dimensions of risk recommended by Iezzoni [27] that are most likely to explain the variation in mortality. Such variables should not only include patient characteristics, recent health status, mental acuity and quality of life, but also markers of acute clinical stability.

Future Directions

We present an example of our dynamic nomogram on line [28]but emphasize that, based on our global model, that prediction can be improved with recruitment of more patients. While this study identifies important risk factors for mortality in hip fracture patients, and robustly demonstrates proof of concept for an app-based dynamic nomogram of individualized mortality risk, medical apps must be registered with the MHRA as Class 1 medical devices prior to any clinical use, which requires prospective registration of data gathering. Our app is not registered and should not be used to guide specific patient treatment: the prototype app provided on-line is for educational

purposes and to inform future research. As such, validation against a larger patient population is needed to validate the model and support a future application for MHRA device registration.

Conclusion

We developed a dynamic nomogram for prediction of survival using Shiny that presents CPH, logistic and binomial models in an easy, intuitive and interpretable format. All models identified lactate, creatinine on admission as independent predictors of mortality.

Although our relatively small numbers limit external application at this juncture, it, nevertheless emphasizes that acute hemodynamic changes drive mortality not just in the first 30 days, but also up to one year after operation.

Acknowledgments

Nil

Competing interests

G M is a member of the BBraun/Philips scientific advisory panel and has received funding for presentation of research at international meetings.

References

1. Physicians. RCo. National Hip Fracture Database annual report. London: 2018.
2. Marufu TC, White SM, Griffiths R, Moonesinghe SR, Moppett IK. Prediction of 30-day mortality after hip fracture surgery by the Nottingham Hip Fracture Score and the Surgical Outcome Risk Tool. Anaesthesia. 2016 May;71(5):515-21. PMID: 26940757. doi: 10.1111/anae.13418.
3. Pincus D, Ravi B, Wasserstein D, Huang A, Paterson JM, Nathens AB, et al. Association Between Wait Time and 30-Day Mortality in Adults Undergoing Hip Fracture Surgery. JAMA. 2017 Nov 28;318(20):1994-2003. PMID: 29183076. doi: 10.1001/jama.2017.17606.
4. White SM, Moppett IK, Griffiths R, Johansen A, Wakeman R, Boulton C, et al. Secondary analysis of outcomes after 11,085 hip fracture operations from the prospective UK Anaesthesia Sprint Audit of Practice (ASAP-2). Anaesthesia. 2016 May;71(5):506-14. PMID: 26940645. doi: 10.1111/anae.13415.
5. Menendez-Colino R, Alarcon T, Gotor P, Queipo R, Ramirez-Martin R, Otero A, et al. Baseline and pre-operative 1-year mortality risk factors in a cohort of 509 hip fracture patients consecutively admitted to a co-managed orthogeriatric unit (FONDA Cohort). Injury. 2018 Mar;49(3):656-61. PMID: 29329713. doi: 10.1016/j.injury.2018.01.003.
6. Kim BG, Lee YK, Park HP, Sohn HM, Oh AY, Jeon YT, et al. C-reactive protein is an independent predictor for 1-year mortality in elderly patients undergoing hip fracture surgery: A retrospective analysis. Medicine (Baltimore). 2016 Oct;95(43):e5152. PMID: 27787371. doi: 10.1097/MD.0000000000005152.
7. Jalali A, Alvarez-Iglesias A, Roshan D, Newell J. Visualising statistical models using dynamic nomograms. PLoS One. 2019;14(11):e0225253. PMID: 31730633. doi: 10.1371/journal.pone.0225253.
8. Zhou X, Ning Q, Jin K, Zhang T, Ma X. Development and validation of a preoperative nomogram for predicting survival of patients with locally advanced prostate cancer after radical prostatectomy. BMC Cancer. 2020 Feb 4;20(1):97. PMID: 32019501. doi: 10.1186/s12885-020-6565-5.
9. Harrell F. Regression Modeling Strategies. 2nd ed. Heidelburg, : Springer; 2015.
10. Griffiths R, Babu S, Dixon P, Freeman N, Hurford D, Kelleher E, et al. Guideline for the management of hip fractures 2020: Guideline by the Association of Anaesthetists. Anaesthesia. 2021 Feb;76(2):225-37. PMID: 33289066. doi: 10.1111/anae.15291.
11. Munirama S, McLeod G. 'Stratified' approach to individualized anaesthetic care. Br J Anaesth. 2015 Apr;114(4):543-5. PMID: 25296913. doi: 10.1093/bja/aeu345.
12. Karres J, Heesakkers NA, Ultee JM, Vrouenraets BC. Predicting 30-day mortality following hip fracture surgery: evaluation of six risk prediction models. Injury. 2015 Feb;46(2):371-7. PMID: 25464983. doi: 10.1016/j.injury.2014.11.004.
13. Tilkeridis K, Ververidis A, Kiziridis G, Kotzamitelos D, Galiatsatos D, Mavropoulos R, et al. Validity of Nottingham Hip Fracture Score in Different Health Systems and a New Modified Version Validated to the Greek Population. Med Sci Monit. 2018 Oct 27;24:7665-72. PMID: 30367027. doi: 10.12659/MSM.909943.
14. Guzon-Illescas O, Perez Fernandez E, Crespi Villarias N, Quiros Donate FJ, Pena M, Alonso-Blas C, et al. Mortality after osteoporotic hip fracture: incidence, trends, and associated factors. J Orthop Surg Res. 2019 Jul 4;14(1):203. PMID: 31272470. doi: 10.1186/s13018-019-1226-6.

15. SIMD. [28th January 2021]; Available from: https://www.gov.scot/publications/scottish-index-multiple-deprivation-2016/pages/5/
16. [Accessed 28th January 2021]; Available from: https://www.gov.scot/publications/scottish-index-multiple-deprivation-2016/pages/5/
17. Venkatesan M, Smith RP, Balasubramanian S, Khan A, Uzoigwe CE, Coats TJ, et al. Serum lactate as a marker of mortality in patients with hip fracture: A prospective study. Injury. 2015 Nov;46(11):2201-5. PMID: 26337798. doi: 10.1016/j.injury.2015.06.038.
18. Chen X, Zhang J, Zhang Y, Lin Y, Liu Z, Wang X, et al. Serum lactate concentration on admission to hospital predicts the postoperative mortality of elderly patients with hip fractures 30 days after surgery. Am J Transl Res. 2021;13(9):10363-71. PMID: 34650704.
19. Uzoigwe CE, Venkatesan M, Smith R, Burnand HG, Young PS, Cheesman CL, et al. Serum lactate is a prognostic indicator in patients with hip fracture. Hip Int. 2012 Sep-Oct;22(5):580-4. PMID: 23112077. doi: 10.5301/HIP.2012.9762.
20. Salottolo KM, Mains CW, Offner PJ, Bourg PW, Bar-Or D. A retrospective analysis of geriatric trauma patients: venous lactate is a better predictor of mortality than traditional vital signs. Scand J Trauma Resusc Emerg Med. 2013 Feb 14;21:7. PMID: 23410202. doi: 10.1186/1757-7241-21-7.
21. Haas SA, Lange T, Saugel B, Petzoldt M, Fuhrmann V, Metschke M, et al. Severe hyperlactatemia, lactate clearance and mortality in unselected critically ill patients. Intensive Care Med. 2016 Feb;42(2):202-10. PMID: 26556617. doi: 10.1007/s00134-015-4127-0.
22. Akinleye SD, Garofolo G, Culbertson MD, Homel P, Erez O. The Role of BMI in Hip Fracture Surgery. Geriatr Orthop Surg Rehabil. 2018;9:2151458517747414. PMID: 29468090. doi: 10.1177/2151458517747414.
23. Hjelholt TJ, Johnsen SP, Brynningsen PK, Knudsen JS, Prieto-Alhambra D, Pedersen AB. Development and validation of a model for predicting mortality in patients with hip fracture. Age Ageing. 2021 Dec 6. PMID: 34923589. doi: 10.1093/ageing/afab233.
24. Chen CY, Chen YF, Chen HY, Hung CT, Shi HY. Artificial Neural Network and Cox Regression Models for Predicting Mortality after Hip Fracture Surgery: A Population-Based Comparison. Medicina (Kaunas). 2020 May 19;56(5). PMID: 32438724. doi: 10.3390/medicina56050243.
25. Moppett I. Accuracy of POSSUM and Nottingham Hip Fracture Score. Acta Anaesthesiol Scand. 2018 Oct;62(9):1333-4. PMID: 29963689. doi: 10.1111/aas.13201.
26. Forssten MP, Bass GA, Ismail AM, Mohseni S, Cao Y. Predicting 1-Year Mortality after Hip Fracture Surgery: An Evaluation of Multiple Machine Learning Approaches. J Pers Med. 2021 Jul 27;11(8). PMID: 34442370. doi: 10.3390/jpm11080727.
27. Iezzoni LI. The risks of risk adjustment. JAMA. 1997 Nov 19;278(19):1600-7. PMID: 9370507. doi: 10.1001/jama.278.19.1600.
28. https://hip-fracture-modelling.shinyapps.io/hip-fracture-modelling/.

Supplementary Files

Figures

Fig 1.Cox proportionality survival model up to 365 days after hip fracture surgery. Hazard ratios show reduced risk of death with increasing age and reduced BMI. Risk of death rose with increased creatinine and lactate levels. Note the non-linear increase in risk with creatinine, and the increase in risk from values immediately above the physiological range.

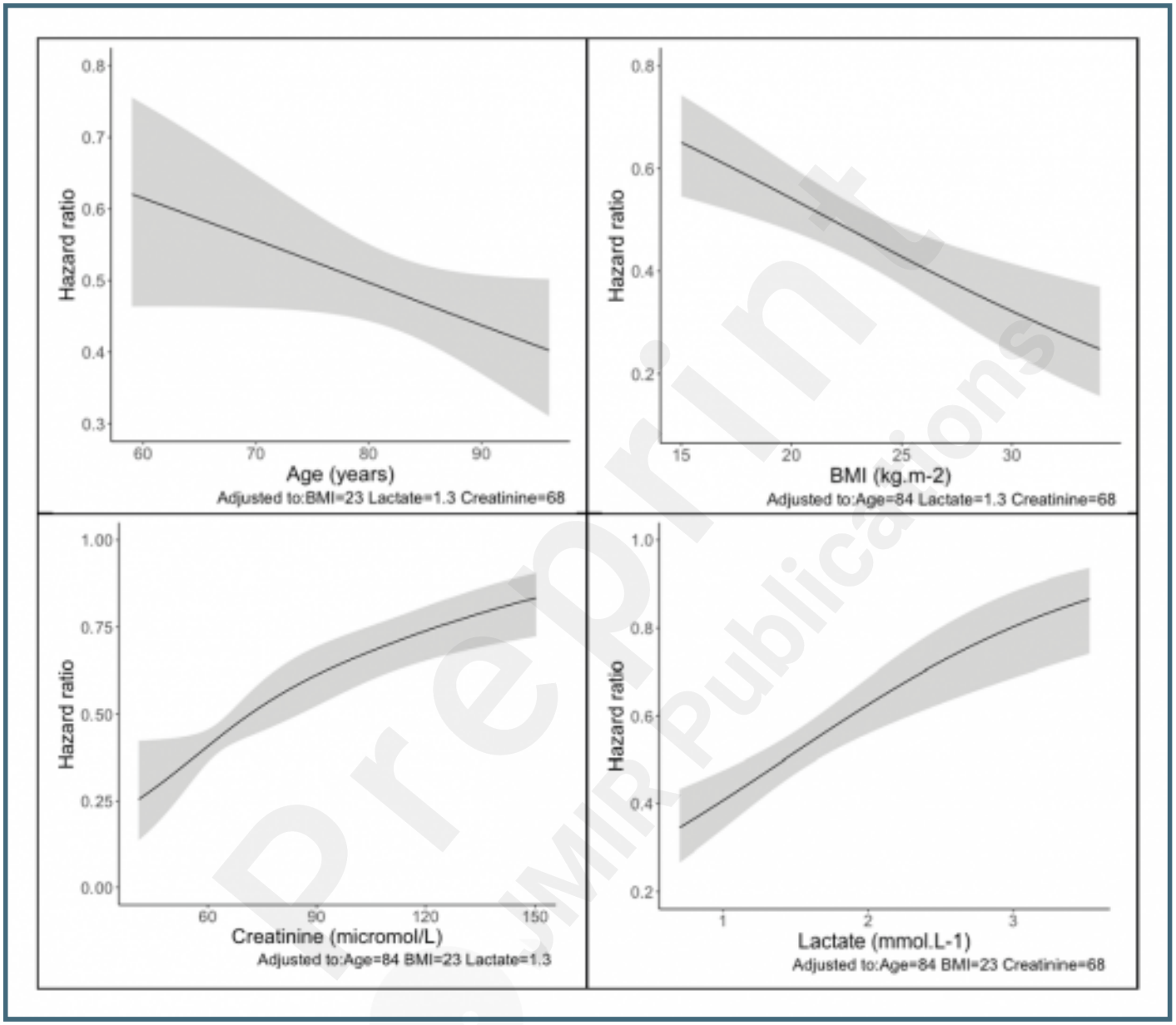


Fig 2 Dynamic Nomogram. Image (a) shows sliders that are used to enter data for Age standardized to 80 years and WCC = 10 (109 .L-1). Four imaginary scenarios presented differing in BMI, creatinine and lactate. Red line: BMI 25 kg.m-2 Creatinine 80?mol.L-1 , lactate 1.5 mmol.L-1 Green line: BMI 15 kg.m-2 creatinine 80 ?mol.L-1 , lactate 1.5mmol.L-1 Blue line: BMI 15 kg.m-2 creatinine 80 ?mol.L-1 , lactate 4 mmol.L-1 Purple line: BMI 15 kg.m-2 creatinine 140 ?mol.L-1 , lactate 4 mmol.L-1 Dynamic nomogram available at: https://hip-fracture-modelling.shinyapps.io/hip-fracture-modelling/.