PREDICTING OUTCOMES IN CRITICALLY ILL CANADIAN OCTOGENARIANS

A Manuscript Thesis Submitted in Partial Fulfillment of the Requirements for the Master of Science in Epidemiology, School of Epidemiology, Public Health and Preventative Medicine, University of Ottawa

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Thesis Committee Members:
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Legend (in order of appearance in text)

ICU—Intensive Care Unit, a specialized clinical area that provides advanced care for the sickest patients in a hospital

Elderly / Very Old—For the purposes of this paper refers to patients 80 years of age and older

Critically Ill—Patients with life threatening illnesses who are considered for ICU admission

Realistic 80—Realities, Expectations and Attitudes to Life Support Technologies in Intensive Care for Octogenarians, an observational study conducted at 22 Canadian Hospitals between September 2009 and February 2013. Provides the data for these manuscripts.

Apache II—Acute Physiology and Chronic Health Evaluation, a scoring system measured on ICU Day 1 that incorporates 12 routine physiologic measurements and is used to describe severity of illness and to predict mortality

SOFA—Sequential Organ Failure Assessment Score, a scoring system that is used to track a patient's organ function. It is based on six different organ function scores: respiratory, cardiovascular, neurologic, hematologic, renal and hepatic.

Life Support / Life Sustaining Therapy / Life Prolonging Technology—Advanced forms of treatment that use machines to replace or support the function of failing organs.

Mechanical Ventilation—A form of life support for assisting / replacing the respiratory system. It can be invasive (using a tube placed in patients' tracheas), or non-invasive by connecting to patients through tight fitting facial masks.

Central Venous Access—The placement of large cannulas into the deep veins that lead directly to the right side of the heart.

Vasoactive Medications—Medicines that stimulate blood vessels to constrict, the heart to beat more powerfully and / or stronger, or both.

(C)RRT—(Continuous) Renal Replacement Therapy, a form of dialysis to replace the function of the kidney. Can be continuous or intermittent.

CCCTG—Canadian Critical Care Trials' Group, an assembly of Canadian ICU physician-researchers who meet three times a year to collaborate on ICU research projects.

HRQOL—Health Related Quality of Life, a multi-dimensional concept that measures physical, mental, emotional and social functioning.

Charleson Comorbidity Index—A measure of the number of medical problems that a patient has, in addition to the reason for their current presentation.

Functional Comorbidity Index—A score used to predict physical functioning using medical comorbidity data.

BMI—Body Mass Index, a measure of the ratio of patient weight to height

GCS—Glasgow Coma Score, a measure of patient alertness comprised of 3 scores: eye responsiveness, motor responsiveness and verbal responses.

Acknowledgements

As a first year medical student during the summer of 1999 I was fortunate enough to work both clinically and academically with Dr. Ian Stiell. Sixteen years, an MD, a residency, and two fellowships later he continues to provide excellent mentorship during what I (and my wife) hope will be the last part of my formal education. Dr. Stiell helped me to secure a position in the University of Ottawa MSc program, is always available for feedback, and has been an invaluable source of experience and good judgement through many practical challenges along the way. He will always be thought of with great fondness for his continued support during my medical training.

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Above all, I would like to acknowledge my wife Mary. She has stood by me, encouraged me, and moved cities (twice) for my training. My deepest thanks to my wife Mary and our children Alyssa, Kiera, Ryan and Kyle.

Contribution of Authors

Master's In Clinical Epidemiology Candidate

I am the principal author of the three manuscripts contained in this Master's of Epidemiology manuscript thesis. I conceived the ideas for the manuscripts, and take full responsibility for the data analysis within them. Being an epidemiology student, naturally I received support with the more complex statistical analysis and methodologic decision making. I understand and can defend the rationale behind the clinical prediction rule derivations contained within this thesis. In addition, I will be the first author of these manuscripts when they are submitted for publication.

Supervisor

Dr. Ian G Stiell is Chair of the Department of Emergency Medicine at the University of Ottawa, Chair of Emergency Medicine Research at the Ottawa Health Research Institute, Senior Scientist at the Ottawa Health Research Institute Clinical Epidemiology Unit, and a Member of the School of Graduate Studies and Research at the University of Ottawa. Dr. Stiell is a world expert in the field of clinical decision rules. His role was to provide guidance regarding biostatistical technique selection, clinical content expertise, manuscript review, and overall project supervision. Dr. Stiell will be the senior author when the manuscripts are submitted for publication.

Advisory Committee

Dr. George A. Wells is a member of the Faculty of Graduate and Postdoctoral Studies. His role was to provide the biostatistical support for the development of the decision rule. Dr. Wells also provided guidance with regard to the methodological design of the prediction rule, ease of clinical applicability and thesis manuscript editing. Dr. Wells has supervised other graduate theses involving prediction rule work. He has published extensively in the area of clinical prediction rules. Dr. Wells will be a co-author when these manuscripts are submitted for publication.

Dr. Daren K Heyland is a Professor of Medicine and Epidemiology at Queen's University and Director of the Clinical Evaluation Unit at Kingston General Hospital. Dr. Heyland is a world expert in the field of end of life care. His role will be to provide guidance regarding content expertise, and manuscript review. Dr. Heyland was the PI on the Realistic 80 research trial. Due to unforeseen circumstances, Dr. Heyland had to withdraw from his position on this thesis committee as of March, 2015.

Preface

The REALISTIC-80 Study (Realities, Expectations and Attitudes to Life Support Technologies in Intensive Care for Octogenarians), clinicaltrials.gov NCT01293708 was a multicenter, prospective, observational cohort study conducted from September 2009 to February 2013. Twenty two Canadian academic and community ICUs participated. Waived consent was obtained from each local Research Ethics Board. All patients over eighty years old who were admitted to ICU were eligible. The principal manuscript from this study has been recently published.[30] The principal manuscript evaluated differences between participants who stayed in ICU for longer than 7 days versus those who stayed for less than 7 days, outcome differences based on pre-morbid frailty scores, and management and outcome differences based on the presence or absence of advanced directives. Our descriptive paper (Manuscript 1) focuses on differences in processes of care, ICU and hospital lengths of stay, mortality, and disposition, between medical patients and surgical emergency patients. Manuscript 1 was written completely independently of Realistic 80's principal manuscript.

The conception, design, ethics applications, grant submissions and data collection for Realistic 80 were already complete or well underway when I began my MSc and my thesis. I was not involved in any part of these aspects of the study. I cleaned the data for clinical discrepancies (after a research assistant had completed the cleaning for typographic errors, duplications, etc.), conceived the three manuscripts, performed the data analysis, interpreted the analysis, and wrote all three manuscripts. Drs. Stiell and Wells guided many of the data analysis strategies, as I have indicated throughout the thesis. Dr. Stiell reviewed the thesis with me.

Thesis Abstract

Background: Based on survey data from both Canada and abroad, most people would prefer to be cared for and to die in their own homes. Although 70% of elderly patients state a preference for comfort care over high technology life prolonging treatment in an inpatient setting, 54% are still admitted to intensive care units (ICUs). Understanding their wishes regarding end-of-life care, and being able to engage in evidence informed end-of-life discussions has never been so important, in order to empower patients, and to optimize scarce resource management. For the purpose of this thesis, "very old" patients will be defined as those eighty years of age and older.

All three manuscripts will be based on data from the Realistic 80 study, a prospective cohort trial of 1671 critically ill very old patients admitted to 22 Canadian ICUs.

Objectives:

Manuscript 1: To describe the hospital outcomes of the entire cohort of Realistic 80 patients, including their ICU mortality and length of stay, their hospital mortality and length of stay, and their ultimate dispositions.

Manuscript 2: To derive a clinical prediction rule for hospital mortality in the medical patient cohort.

Manuscript 3: To derive a clinical prediction rule for hospital mortality in the emergency surgical patient cohort.

Data Source: A prospective, multicenter cohort study of very elderly medical and surgical patients admitted to 22 Canadian academic and non-academic ICUs.

Methods: Clinical decision rule methodology was used to analyze the data set and to

create two separate clinical prediction tools, one for critically ill elderly medical patients, and one for critically ill surgical emergency patients. A third manuscript describing general clinical outcomes was also produced.

Results of Manuscript 1: A total of 1671 patients were included in this section of the "**R**ealities, **E**xpectations and **A**ttitudes to **L**ife **S**upport **T**echnologies in **I**ntensive **C**are for Octogenarians: The Realistic 80 Study (a prospective cohort of nearly 2000 critically ill Canadian patients over eighty years old enrolled from 22 ICUs across Canada) that will provide the data for this thesis.
The Realistic 80 cohort had a mean age of 84.5, a baseline Apache II score of 22.4, a baseline SOFA score of 5.3, an overall ICU mortality of 21.8%, and an overall hospital mortality of 35%. The cohort had a median ICU length of stay of 3.7 days, and an overall median hospital length of stay of 16.6 days. Only 46.4% of the survivors were able to return home to live.

Results of Manuscript 2: Age, renal function, level of consciousness, and serum pH were the important predictors of hospital mortality in critically ill elderly medical patients. Our clinical prediction tool is very good, particularly at the all-important extremes of prognosis, and ready for external validation.

Results of Manuscript 3: Renal function and serum pH were the important predictors of hospital mortality in critically ill elderly surgical patients. Our model's performance is very good, and will serve to inform clinical practice once validated.

Conclusions: Very old medical patients have longer ICU stays and higher mortality than their surgical counterparts. Premorbid health status and severity of illness are associated with mortality. Our medical patient clinical prediction tool is very good and ready for external validation. Our surgical emergency clinical prediction tool shows promise, but will require the incorporation of more patients and a repeat derivation phase prior to external validation or clinical implementation.

Abstrait

Contexte: Au Canada et à l'étranger des enquêtes ont indiqué que la plupart des gens préféreraient être soignés et de mourir dans leurs propres maisons. Malgré que 70% des patients âgés indiquent une préférence pour les soins de confort plutôt qu'avoir la vie prolonger par des traitements d'haute technologie dans un milieu hospitalier, 54% sont encore admis aux unités de soins intensifs (USI). Comprendre leurs souhaits en matière de soins de fin de vie, et d'être capable de participer à des discussions informées sur des données probantes en fin de vie n'a jamais été aussi important. Le but est de responsabiliser les patients et d'optimiser la gestion des ressources rares. Dans cette thèse, " très vieux " patients seront définis comme les quatre-vingts ans et plus.

Tous les trois manuscrits seront basés sur les données de 'Realistic 80 Study', un procès de cohorte prospective de 1,671 gravement malades très vieux patients admis à l'USI de vingt-deux centres canadien.

Objectifs

Manuscrit 1: Pour décrire les résultats des hôpitaux de l' ensemble de la cohorte de 'Realistic 80 Study', y compris leur taux de mortalité de soins intensifs et la durée du séjour à USI, leur taux de mortalité et la durée du séjour à l'hôpital, et leurs dispositions ultimes .

Manuscrit 2: Pour tirer une règle de prédiction clinique pour la mortalité à l'hôpital dans la cohorte de patients médicaux.

Manuscrit 3: Pour tirer une règle de prédiction clinique pour la mortalité à l'hôpital dans la cohorte de patients des soins chirurgicaux d'urgence.

Source des données: Une étude de cohorte prospective, multicentrique de patients médicaux et chirurgicaux très âgés admis à 22 unités de soins intensifs universitaire et non-universitaire canadien.

Méthodes: La méthode de règle de décision clinique a été utilisé pour analyser l'ensemble des données et de créer deux outils de prédiction cliniques distincts. Un pour les patients gravement malades médicaux âgées, et un autre pour les patients des urgences chirurgicales gravement malades. Un troisième manuscrit décrivant les résultats cliniques généraux a également été produit.

Résultats de Manuscrit 1: Un total de 1,671 patients ont été inclus dans cette section des '**R**ealities, **E**xpectations and **A**ttitudes to **L**ife **S**upport **T**echnologies in **I**ntensive **C**are for Octogenarians: Le 'Realistic 80 Study' (une cohorte prospective de près de 2,000 patients canadiens gravement malades plus de quatre-vingts ans inscrits à partir de 22 unités de soins intensifs à travers le Canada) qui fournira les données pour cette thèse.

Le 'Realistic 80 Study' avait un âge moyen de 84,5 ans, un score de référence Apache II de 22,4, un score SOFA base de 5,3, un taux de mortalité de l'USI global de 21,8%, et une mortalité hospitalière globale de 35%. La cohorte avait une longueur ICU median de séjour de 3,7 jours, et une longueur moyenne d'hospitalisation global de séjour de 16,6 jours. Seulement 46,4% des survivants ont pu rentrer chez eux pour vivre.

Résultats de Manuscrit 2: La fonction rénale, âge, niveau de la conscience, et le sérum pH étaient les facteurs prédictifs importants de mortalité à l'hôpital dans un état critique patients médicaux âgées. Notre outil clinique prédictif donne une prévision précise, en particulier au niveau des extrêmes de tous les importants de pronostic, et prêt pour une validation externe.

Résultats de Manuscrit 3: La fonction rénale et le sérum pH étaient les facteurs prédictifs importants de mortalité à l'hôpital chez les patients chirurgicaux âgées

gravement malades. Notre modèle prédit avec précision et de manière faible la performance des patients, et servira à éclairer la pratique clinique une fois validé.

Conclusions: Les patients médicaux très vieux ont des séjours de plus en plus longs aux soins intensifs et une mortalité plus élevée que leurs homologues chirurgicales. L'état de santé avant la maladie et la gravité de la maladie sont associés à la mortalité. Notre outil de prédiction clinique médicale du patient est très bon et prêt pour une validation externe. Notre outil de prédiction clinique d'urgence chirurgicale montre promesse, mais il aura besoin l'incorporation d’un plus grand nombre de patients et une phase de dérivation de répétition avant la validation des outils externe ou la mise en œuvre clinique.

Chapter 1 – Introduction to Realistic 80

Background

The percentage of the world's population that is over 80 years of age is expected to double by 2050.[1-3] Australian data demonstrates a 6% increase per year in ICU admissions for patients over 80 years of age between 2000 and 2005.[4] The same data suggests that by 2015, 25% of ICU admissions will be for patients over 80 years of age. The main causes of death in this demographic group are degenerative diseases and cancer.[5] Twenty percent of these deaths occur in Canadian ICUs[6,7] Patients over the age of 65 currently account for half of ICU admissions and nearly 60% of all ICU days.[8-10] Reserving the use of ICU beds for elderly patients who wish to receive aggressive life sustaining therapies, and are likely to benefit from it, could significantly improve critical care resource allocation and utilization.

Based on survey data from both Canada and abroad, most people would prefer to be cared for and to die in their own homes. In addition, although 70% of elderly patients state a preference for comfort care over high technology life prolonging treatment in an inpatient setting, 54% are still admitted to intensive care units.[10,11]

A 2006 study by Heyland et al. [12] identified that elderly Canadians value quality, not quantity of life, and do not want technology supported life prolonging measures. Canadian ICUs continue to mechanically ventilate and use life prolonging technology in the elderly, even when there is little chance of meaningful recovery. There is currently a significant disconnect between the wishes of the Canadian population and the ground level clinical practice.

A similar challenge was demonstrated in a recent French study that found that although 70% of hospitalized patients over 80 years old wanted comfort care rather than life-prolonging care, 54% were admitted to ICUs.[13]

Data from the United States confirms the existence of the same discrepancy. In the Hospitalized Elderly Longitudinal Project (HELP), although 70% of participants stated a preference for comfort focused care rather than life-prolonging care, and over 80% had a do-not resuscitate order, 63% of patients received one or more life-sustaining treatments before they died.[14]

These discrepancies disrespect patient autonomy, and prolong the dying process at significant expense to health care systems.

Rationale

The Clinical Challenge

Acute care physicians in Canada and in much of the rest of the first world frequently engage in end-of-life discussions regarding goals of care for critically ill very old patients. These discussions may involve patients themselves, their families, substitute decision makers, or some combination of the three. They typically occur in emergency departments in the acute phase of a critical illness, or on hospital wards when patient conditions deteriorate unexpectedly. To make matters worse, the physicians involved may be meeting the patient and their family for the first time, or may have known them for only a very short time.

The discussions revolve around what the goals of care should be: curative or palliative. As mentioned above, a large proportion of critically ill very old patients end up receiving treatments (such as ICU admission and / or life support in the form of mechanical ventilation [invasive or non-invasive], central venous access, vasoactive medication administration, and / or renal replacement therapy) that are more

aggressive and invasive than they desire. In many circumstances, not only does the institution of these therapies violate patient autonomy, but it often prolongs the dying process, rather than offering any meaningful chance of recovery.

Lastly, inappropriate use of critical care beds wastes scarce resources, at significant expense to the health care system.

Reasons for Inappropriately Aggressive Treatment

There are many reasons for the discrepancy between patients' previously articulated treatment wishes and ground level practice.

Patients and their decision makers are untrained and unaccustomed to making life and death decisions. Asking them to do so during a time of critical illness, even if only to reconfirm previously expressed wishes, subjects them to duress. In many instances they are fearful of death, and / or reluctant to be seen as "giving up", rather than "fighting through" their illness. Some authors have suggested that the often used metaphor comparing illness to a battleground is completely inappropriate, and places undue pressure on patients and their substitute decision makers.(15)

In a society that is increasingly driven by high levels of technology and "quick fixes", lay people and health care providers alike are often reluctant to deny patients high technology treatments. Health care workers often remark that the elderly are rarely allowed to "die of old age" anymore. So many levels of therapy are available that physicians rarely tell patients the old saying: "There is NOTHING more that we can do…."

But just because we can, doesn't mean that we always should. There is an important difference between doing something *for* a patient versus doing something *to* them. Health care providers and patients alike may fear death, and despite not liking the idea of intensive care and aggressive life sustaining therapies, when faced with death as an alternative, they elect for ICU admission. As previously mentioned, this decision is one

that patients and their families have been shown to later regret. Furthermore, it may lead to a technology supported, institutionalized death that lasts days to weeks, and is seen by some as unnecessary, undignified, and even inhumane, particularly when lifesaving therapy was futile all along.

Most importantly of all, there is little data to guide decision makers regarding appropriate goals of care for the very old with critical illness. During goals of care discussions, clinicians are often asked to prognosticate on likely outcomes should aggressive life support be instituted. Many reasonable decision makers would opt for palliative care if they were given a very poor prognosis. Conversely, decision makers might more appropriately change their code status and agree to a brief course of life support given a favorable prognosis and a short term ICU and hospital stay.
It seems only reasonable that the goal should be to align therapy to both the patients' informed wishes, and to the expected clinical course.

This concordance is optimized by the availability of evidence based, robust clinical prediction rules that have been derived and prospectively validated in similar populations to that of the individual patient to which they are being applied. This is the objective of the two prediction rule manuscripts contained within this thesis.

Clinical Prediction Rule Methodology

Multiple sources in the medical literature describe techniques for clinical decision / prediction rule creation (the science behind the development of a clinical decision rule is similar to that for the development of a prediction rule but the term "prediction rule / tool" will be used throughout this thesis since that is the ultimate goal).[16-19] Stiell et al. described six phases to be considered for the development of a new prediction rule:[18]

1) **identification** of clinical need (i.e. is there a wide practice variation and / or

poor clinician consensus / sparse literature or practice guidelines?) Is the clinical scenario in question common enough to warrant the tremendous effort necessary to produce a robust, scientifically derived and validated prediction rule?

2) **derivation phase**: identification (ideally through a prospectively collected data set obtained specifically for the purpose of rule derivation) of variables obtained from patient history, prior medical conditions, clinical examination, and / or diagnostic tests that have high interobserver reliability and are practical and simple for clinicians to recall and utilize.

3) **validation phase**: an evaluation of rule performance (sensitivity, specificity, positive and negative predictive values). The validation phase is strengthened when performed on a new set of patients, by different clinicians, in different clinical settings from which the rule was derived.[20]

4) **implementation phase**: to demonstrate the impact and penetration of the rule into routine clinical practice.

5) **economic analysis:** to evaluate the financial implications of rule implementation.

6) **dissemination phase:** once the first five phases suggest that a robust, financially advantageous rule has been generated, this phase includes strategies for knowledge translation to relevant audiences.

Steps in Prediction Rule Creation

Patient information including demographics, previous medical history, clinical examination findings, and diagnostic test results comprise the independent covariates. Ideally, this data should be collected prospectively, and specifically as part of a research endeavor whose objective is the derivation of a clinical prediction rule. The covariates

to be included in the modeling should be identified prior to data collection by a group of clinical experts. Priorities to be considered when choosing covariates include: clinical importance, widespread emergency department and hospital ward availability in a timely manner, high interobserver reliability, and ease of use.

Predictors can be gathered from a clinical trial dataset or database, but this is less desirable. The least desirable means for acquiring data is retrospectively from administrative or health records databases. The likelihood of missing data and recording bias increases across the above three modalities.

Irrespective of the means used to gather the covariates, once they are selected, univariate logistic regression is performed to identify predictors highly correlated with mortality. In the initial step, continuous variables are analyzed as such. Predictors showing no association ($P > 0.2$) with the outcome are generally discarded. Continuous predictors with P values that are **less 0.2, *or above 0.2 but felt to be clinically important***, are "cut" at clinically meaningful points to create categorical variables. These categorical variables are re-analyzed in a univariate regression model.

There are practical considerations to predictor selection as well. Practical considerations include the availability of information to health care workers at the time of patient presentation to hospital, inter observer reliability, and likely willingness of patients to undergo the investigation.

Predictors that are associated with the outcome, and have high availability, interobserver reliability, and are likely to be acceptable to clinicians, will be used for the multivariable analysis. Prediction rules can be designed to be dichotomous, (i.e. does this patient with traumatic knee pain presenting to the emergency department require a knee x-ray?) or to give a probability estimate of the occurrence of an outcome of interest (i.e. ICU mortality). In the case of this thesis, the latter strategy will be employed.

A standard rule of thumb is that the derivation dataset should contain at least ten outcomes per predictor variable.[18,20] The desired sensitivity and 95% confidence intervals of the rule, combined with the incidence of the primary outcome, will dictate the sample size necessary for rule derivation.

As previously mentioned, the first step in rule generation involves evaluation of predictor variables using univariate analyses. This step will select a list of patient factors that are strongly correlated with the primary outcome. The subsequent step utilizes multivariate logistic regression and / or recursive partitioning. The final prediction rule is derived by optimizing the results of the multivariate analysis, with sensitivity, interobserver reliability, and practical considerations (i.e. ease of rule recall, acceptability to clinicians, etc.)

Once the derivation phase of the prediction rule is complete, a validation phase is necessary. The validation phase may be performed on the *same* sample from which the rule was derived. However, a prospective validation in a *different* sample of patients, by different clinicians, at different centers from which the derivation phase was performed optimizes the robustness of the rule, as well as its acceptability and eventual widespread clinical use by practitioners.[16,20]

In order to improve the likelihood of a clinical prediction rule manuscript's acceptance for publication, some form of validation phase is required. A prospective validation on a new patient sample will require successful funding applications, and several years of patient enrollment. This cannot be accomplished within the confines of this Master's thesis. Our clinical prediction rules will be validated on the same sample from which they are derived, by bootstrapping.

After the thesis is complete, an application to granting agencies for external funding to perform a prospective validation in a new sample of patients will be submitted.

Overall Goals

The primary objective of this thesis is to derive a clinical prediction rule for ICU mortality in Canadian octogenarians, separately for medical and surgical patients. This rule will be based on clinical variables that will be available to patients, their family members / surrogate decision makers, and acute care physicians **prior to a decision regarding ICU admission.** The prediction rule will incorporate data from patient history, premorbid medical conditions, clinical examination findings, and diagnostic tests results.

The incorporation (by acute care clinicians) of the final prediction rule along with patient and family preferences will improve end-of-life decision making by very old patients, their families, and their clinicians. Providing evidence based information will empower decision makers, enhance their ability to protect patient autonomy, and optimize utilization of health care resources.

What is Realistic 80?

This thesis will use the Realistic 80 dataset to create the clinical prediction rules. "**R**ealities, **E**xpectations and **A**ttitudes to **L**ife **S**upport **T**echnologies in **I**ntensive **C**are for Octogenarians: The Realistic 80 Study" is a prospective, multicenter, observational study of 1671 patients enrolled at twenty-two Canadian centers between September 2010 and February 2013. It followed patients for one year after their ICU admission to evaluate study outcomes.

Realistic 80 was conducted under the auspices of the Canadian Critical Care Trials Group (CCCTG) and the Canadian Critical Care Society (CCCS) in association with the Canadian Researchers at the End of Life Network (CARENET). It was funded by a Canadian Institutes of Health Research (CIHR) grant. Realistic 80's goal is to collect data surrounding the cohort of octogenarians admitted to Canadian ICUs with the objective of using this information to improve end of life care.

Realistic 80's primary investigator and CIHR grant recipient was Dr. Daren Heyland. He has agreed to allow unlimited access to the Realistic 80 dataset for myself and my thesis committee members. Although the Realistic 80 study was conceived and designed outside of my thesis, the data verification phase, covariate evaluation and selection, univariate analysis, multivariate logistic regression, and manuscript preparation were all performed within the context of this thesis project.

Through this Master's thesis, the relationship between patient factors (comorbidities, vital signs, investigation results) and their outcome data will be evaluated. Realistic 80's primary research question was: "What are the 12-month health related quality of life (HRQOL), functional status, and survival of patients admitted to ICU who are 80+ years old?"

Its secondary research question was: "Which patient characteristics are associated with 12-month HRQOL, functional status, and survival?"

Realistic 80 Study Population

Patients over 80 years of age admitted to participating ICUs were all considered for study enrollment. Exclusion criteria included inability to communicate in English or French (directly or through a family or friend), not having a permanent address, or not being a resident of Canada. Patients not having a family caregiver were also excluded.

Potential Regression Model Variables

The following baseline demographic information was collected on all patients enrolled in Realistic 80. Each component of these measures will be considered as an independent variable in a regression model:

Potential Regression Model Variables	
i.	Age
ii.	Sex
iii.	Marital status
iv.	Living status (alone, with someone at home, supervised residential setting, nursing home, other)
v.	Acute Physiologic And Chronic Health Evaluation 2 (APACHE 2) [calculated from 12 routine physiologic measurements]
vi.	Baseline Sequential Organ Failure Assessment score (SOFA) [an ICU scoring system used to track the extent of patients' organ function that is based on six organ scores, one each for cardiovascular, respiratory, neurologic, hepatic, coagulation and renal]
vii.	Type of ICU Admission (medical / elective surgical / emergency surgical)
viii.	Following chronic, declining illness vs. acute onset of illness
ix.	Hospital length of stay prior to ICU admission
x.	Primary ICU diagnosis as per APACHE 2 taxonomy
xi.	Charleson Comorbidity score
xii.	Functional Comorbidity Index
xiii.	Number of hospitalizations in the past 12 months
xiv.	Number of emergency department visits in the past 12 months
xv.	Number of ICU admissions in the past 12 months
xvi.	Body Mass Index
xvii.	Pre-hospital serum albumin

Outcome Measures

All cause hospital mortality is the primary outcome of the observational component (Manuscript 1 of this thesis) of Realistic 80.

Secondary endpoints include: ICU length of stay, hospital length of stay, ability to return to previous level of living / functioning, SOFA scores.

Sample Size—Medical Patients

Based on previous publications that evaluated the effect of age on ICU survival [11,13,14,21-24], the hospital mortality was expected to be approximately 40%. Given a study sample size of 1600 patients, there should be 1600 x 0.4 = 400 patients sustaining the primary outcome, hospital mortality. By the rule of thumb suggesting that a minimum of ten outcomes are necessary per covariate [18,20,25], the Realistic 80 database includes ample numbers of patients sustaining the primary outcome to produce a robust clinical prediction rule.

Validation

For the purposes of manuscript preparation, and to increase the likelihood of publication, internal validation of the derived prediction rule will be performed using bootstrap resampling. One thousand samples will be selected with replacement of equal size to the final sample size used for derivation. As previously mentioned, the external validation of our prediction rule will be performed *outside* the confines of this MSc thesis. The prospective validation phase is merely a discussion at this point in time. A team of investigators needs to be assembled, a protocol needs to be established, and funding needs to be secured before this phase moves towards patient recruitment. I mention it here to make reviewers aware that I recognize the importance of prospective validation prior to clinical implementation.

Attributes of a Functional Prediction Rule

By clinical means alone, physicians' predictions of patients' mortality risk have been shown to be poor. [16] Published prediction rules show a wide range of accuracy.[16] Larger sample sizes, higher patient mortality, and lower journal impact factor are associated with higher prediction rule accuracy rates.[18]

For implementation into clinical practice a prediction rule should meet the following criteria: validation in a population that is independent from the derivation sample, reproducibility, and good accuracy and calibration.[16]

Additionally, prediction rules ought to be simple. Clinicians are less likely to use tools that require extensive information, or expensive test results. [16] Models with more variables do not necessarily perform better than those with fewer variables.[16]

Convincing some of my co-investigators of the merits of simplicity and a smaller number of predictors has been extremely challenging. There is a sense that more data must be better, and strong encouragement to use complex predictors because they are available. The Apache (Acute Physiology and Chronic Health Evaluation) II score [26] is an example of a prediction tool that has been validated in several different populations.[27]

It is a score that is measured on the first day of ICU admission, and not recalculated again. Apache II consists of the following 12 variables:

APACHE 2 Variables	
1.	AaDO2 or PaO2 (depending on FiO2)
2.	Temperature (rectal)
3.	Mean arterial pressure
4.	pH arterial
5.	Heart rate
6.	Respiratory rate
7.	Sodium (serum)
8.	Potassium (serum)
9.	Creatinine
10.	Hematocrit
11.	White blood cell count
12.	Glasgow Coma Scale

Despite the relative simplicity of Apache II, it is rarely if ever used for clinical prognostication and is reserved almost exclusively for research purposes. For the Realistic 80 prediction rule, we sought to evaluate the components of the Apache II score separately during the univariate analysis, in the hopes that we could derive a more simple rule in the very old critically ill population.

In addition, when reporting component scores for Apache II, the highest and lowest values on the first day are recorded. The original Apache II manuscript [16,28] provides a scoring system that directs researchers regarding which value to use. Points are awarded for increasingly abnormal values. Whichever of the two values is "most abnormal" is the one that should be used for research. This was the practice that we followed for this study.

Chapter 2 – Introduction to Manuscript 1

The objective of Manuscript one is to describe the patient population that was enrolled in the Realistic 80 cohort study, and its subsequent outcomes.

Realistic 80 is the largest prospective study of critically ill very elderly patients. In addition to the demographic information, comorbidities, functional status, and frailty status, novel information gleaned from Manuscript 1 includes mean length of ICU stays, mean length of hospital stays, ICU mortality, hospital mortality, and percentage of patients able to return to independent living.

The Realistic 80 dataset will be used to answer many secondary questions (outside the scope of this thesis), including the following:

1. outcome differences between medical patients, surgical emergency patients, and elective surgical patients (our prediction rules evaluate this question indirectly)
2. morbidity and mortality differences between patients admitted or discharged from the ICU after hours (weekends and evenings) versus during weekday working hours
3. morbidity and mortality differences between elderly males and elderly females
4. differences in treatment goals between elderly males and elderly females
5. outcome differences between younger patients versus older patients (age was one of the predictors that was evaluated in both our medical and surgical emergency prediction rules)

The focus of this thesis is threefold: to describe the one year hospital outcomes of the cohort, to derive a clinical prediction tool for hospital mortality in emergency (unplanned) surgical patients, and to derive a clinical prediction tool for hospital mortality in medical patients.

Based on some preliminary analyses (Tables 1-3), and in discussion with members of the Canadian Critical Care Trials Group at the June 2013 meeting, we decided to analyze medical patients and surgical emergency patients separately.

From a clinician's point of view, the strength of the information contained within Manuscript 1 is its generalizability. It provides outcome data on a large number of very elderly critically ill patients. As mentioned in the introduction, this information will inform end-of-life discussions between clinicians and substitute decision makers **prior to ICU admission.**

From a researcher's perspective, there is an abundance of data that allows for many comparisons and for hypothesis generation to fuel future trials.

Chapter 3 -- Manuscript 1

"Hospital Outcomes of Very Elderly Critically Ill Medical and Surgical Patients: A Multi-Centre Prospective Cohort Study"

Abstract

Background: Very elderly (80 years of age and above) critically ill patients admitted to Medical-Surgical ICUs have a high incidence of mortality, prolonged hospital length of stay, and living in a dependent state should they survive.

Objective: To improve future end-of-life decision making for very elderly patients admitted to Canadian ICUs by reporting short and long term outcomes, thereby informing decision making for clinicians and substitute decision makers.

Methods: A prospective, multicenter cohort study of very elderly medical and surgical patients admitted to 22 Canadian academic and non-academic ICUs. Outcome measures will include ICU length of stay and mortality, hospital length of stay and mortality, and disposition post hospital discharge.

Results: A total of 1671 patients were evaluated. Patient demographics included: mean age of 84.5, baseline Apache II of 22.4, baseline SOFA of 5.3, overall ICU mortality of 21.8%, and overall hospital mortality of 35.0%. Study participants stayed in ICU for a median of 3.7 (IQR 5.8) days, and in hospital for a median of 16.6 (IQR 24.8) days. Only 46.4% of the survivors were able to return home to live.

Conclusions: Although mean ICU and hospital mortalities were not as high as expected, hospital length of stay was long, and less than half of patients were able to return to independent living.

Manuscript

The percentage of the world's population that is over 80 years of age is expected to double by 2050.[1-3] Australian data demonstrates a 6% increase per year in ICU admissions for patients over 80 years of age between 2000 and 2005.[4] The same data suggests that by 2015, 25% of ICU admissions will be for patients over 80 years of age. The main causes of death in this demographic group are degenerative diseases and cancer.[5] Twenty percent of these deaths occur in Canadian intensive care units (ICUs).[6,7] Reserving the use of ICU beds for elderly patients who wish to receive aggressive life sustaining therapies, and are likely to benefit from them, could significantly improve critical care resource allocation and utilization.

Based on survey data from both Canada and abroad, most elderly people would prefer to be cared for and to die in their own homes.[7-9] A 2006 study by Heyland et al.[10,12] identified that elderly Canadians value quality, not quantity of life, and do not want technology-supported life-prolonging measures. Canadian ICUs continue to mechanically ventilate and use life prolonging technology in the elderly, even when there is little chance of meaningful recovery. There is currently a significant disconnect between the wishes of the Canadian population and the ground level clinical practice.[4-7] A similar challenge was demonstrated in a recent French study that found that although 70% of hospitalized patients over 80 years old wanted comfort care rather than life-prolonging care, 54% were admitted to ICUs.[10,11,13] Data from the United States confirms the existence of the same discrepancy. In the Hospitalized Elderly Longitudinal Project (HELP), although 70% of participants stated a preference for comfort focused care rather than life-prolonging care, and over 80% had a do-not resuscitate order, 63% of patients received one or more life-sustaining treatments before they died.[14] These discrepancies disrespect patient autonomy, and prolong the dying process at significant expense to health care systems. The Canadian Critical Care Research Network (CCCRNET) database of over 200 000 ICU admissions demonstrates an increase in the proportion of octogenarian admissions from 10% in 1994 to 14% in

2005. An Ontario (provincial) critical care database demonstrated that from 2006-2008, octogenarians comprised 18% of ICU admissions [28]. Ontario hospital ICU mortality data from 2001-2003 showed that one year after hospitalization, 48% of critically ill octogenarians had died, compared to a 23% ICU mortality in patients under 80 years of age.[20] In a single center, French study published in 2006, 180 critically ill octogenarians were followed to one year post hospital discharge. The hospital and 1 year mortality rates were 63% and 71%. Survivors described higher rates of depression, isolation, and lower mobility than an age and sex matched community cohort. More concerning was the fact that 57% of respondents stated that they would decline a subsequent life sustaining ICU admission in the event of a recurrent critical illness.[29]

There is a sparse amount of Canadian data on outcomes of over 80 year old patients admitted to ICUs. Realistic 80 is the largest prospective study of ICU outcomes on elderly patients. Its prospective nature and rich dataset will allow us to perform multivariable modeling to derive clinical prediction tools to inform goals of care discussions, prior to ICU admission. Our primary objective is to describe the outcomes of the Realistic 80 cohort, including length of ICU stay, ICU mortality, length of hospital stay, hospital mortality, and ultimate disposition. Secondary objectives are to describe the types of very old patients typically being admitted to ICUs, including demographics, admission diagnosis, illness severity, and medical versus surgical causes for admission.

Methods

Design and Setting

The REALISTIC-80 Study (Realities, Expectations and Attitudes to Life Support Technologies in Intensive Care for Octogenarians), clinicaltrials.gov NCT01293708 was a multicenter, prospective, observational cohort study conducted from September 2009 to February 2013. Twenty two Canadian academic and community ICUs participated. Waived consent was obtained from each local Research Ethics Board. All patients over

eighty years old who were admitted to ICU were eligible. The principal manuscript from this study has been recently published.[30] The principal manuscript evaluated differences between participants who stayed in ICU for longer than 7 days versus those who stayed for less than 7 days, outcome differences based on pre-morbid frailty scores, and management and outcome differences based on the presence or absence of advanced directives. Our paper focuses on differences in processes of care, ICU and hospital lengths of stay, mortality, and disposition, between medical patients and surgical emergency patients. A primary motivation for evaluating differences between medical and surgical patients was to justify our decision to derive separate prediction tools

Study Population

We included a consecutive sample of all patients admitted to participating ICUs who were 80 years of age or older. Patients were grouped into 3 categories: elective surgical patients, emergency (unplanned) surgical patients, and medical patients. Enrollment began in September 2009, and was completed in February, 2013. Previously enrolled patients who were re-admitted to the ICU were not re-enrolled, as comprehensive data collection continued for 12 months following the index ICU admission. Routine local practices regarding criteria for ICU admission were maintained.

Baseline Data Collection

Trained research personnel collected data on the following outcomes for each study participant: age, sex, marital status, living status, APACHE II [26], SOFA [31], Functional Comorbidity Index [32], Charlson Comorbidity Index [33], admission type (medical, surgical emergency, surgical elective), following acute or chronic illness, length of hospital stay prior to ICU admission, primary ICU diagnosis, number of hospitalizations and emergency department visits in the preceding 12 months, serum albumin, body mass index, number of days in ICU, number of days in hospital, number of days of mechanical ventilation, and survival.

Survival was defined as able to be discharged from hospital, or alive in hospital one year post ICU admission. Early in the recruitment phase, funding allowed for each site to enroll a convenience sample of the first 60 eligible patients into the hospital cohort. Partway through the trial, this number was decreased to 30 patients per site.

Data Analysis

Continuous variables were described by means, standard deviations, and ranges, with the exception of length of stay variables which were described by medians, quartiles, and ranges because of their positive skews. Categorical variables were described by counts and percentages. All statistical analyses were performed using SAS Version 9.3 (SAS Inc., Cary, NC., USA).

Results

There were 1671 patients enrolled in this study. The majority of study participants were critically ill for medical reasons (1033 patients), while surgical emergencies (418 patients) and elective surgeries (220 patients) formed the remainder of the cohort (Table 1). Consent was waived for this study, so all enrolled patients were successfully followed until either hospital death, 12 months of time had elapsed since their index admission, or they were transferred to a non-study site hospital ward.

The mean age was consistent across the three groups at approximately 84 years. Gender was also very similar among the three groups, with a 55% male distribution. The APACHE II, Charleson and Functional Comorbidity indices were worse in the medical patients, and this result was statistically significant for all three parameters. The SOFA score however, was highest in surgical emergency patients. (Table 1)

The percentage of patients receiving vasopressors was virtually the same in the medical (56.8%), and surgical (54.3%) groups of patients. (Table 2) More than twice as many medical patients (19.3%) received non-invasive mechanical ventilation as

compared to surgical patients (9.8%). (Table 2) This is not unexpected as many more medical patients would be expected to have disease processes that would be amenable to non-invasive ventilatory management. Similarly, many surgical emergency patients are transferred directly to the ICU from the operating room prior to extubation, which likely accounts for the higher proportion of invasively ventilated surgical patients (85.2%), as compared to medical patients (67.1%) (Table 2) More medical patients (7.6%) than surgical patients (4.1%) were willing to receive dialysis at any point during their ICU stay. Medical patients were more likely to have life sustaining therapies withheld at ICU admission, withheld after ICU admission, or withdrawn after ICU admission, as compared to surgical patients (Table 2).

The median total ICU length of stay was 4.1 days in medical patients and 3.8 days in surgical emergency patients (Table 3). Less than seven percent of all patients were readmitted to the ICU. The median total hospital length of stay was 16.2 days and 20.1 days for medical and surgical emergency patients respectively. The ICU mortality was 26.5% in medical patients and 18.7% in surgical emergency patients. The hospital mortality was 41.5% in medical patients and 31.6% in surgical emergency patients (Table 3).

Of the 1086 patients who survived to leave the hospital, 45% of medical patients and 41.6% of surgical emergency patients were able to be discharged home.

Discussion

The results of this study are important at this time for several reasons. The fraction of the population that is very old is increasing at a rapid rate. Increasing numbers of elderly patients are becoming critically ill. Understanding their wishes regarding end-of-life care, and being able to engage in evidence informed end-of-life discussions has never been so important, in order to empower patients, and to optimize scarce resource management.

There is currently a body of literature that attempts to provide data on the outcomes of critically ill elderly patients who are managed aggressively in ICU settings. Boumendil et al. performed a single centre prospective cohort study of 233 octogenarians admitted to a French ICU over a two year period.[16] Their outcome was long term survival and was predicted principally by premorbid patient condition. De Rooij [17] used patient characteristics that were available within first 24 hrs of ICU admission whereas Boumendil used characteristics available within the first 72 hours. Minne's 2011 systematic review evaluated all prognostic models for ICU mortality in elderly patients and concluded that although most of the existing models are methodologically sound, none are ready for implementation into clinical practice.[19]

The lack of robust data about the clinical course of critically ill octogenarians may be a contributing factor to the indecision surrounding end of life care in general, and in Intensive Care Unit admissions specifically.

Canadian acute care physicians are commonly asked by families to quantify the expected mortality rate, prior to any decision regarding the desired level of medical intervention. The default decision by family members when physicians are unable to provide them with an objective, evidence based outcome prediction is often to opt for aggressive, technology driven, life prolonging treatment. This may be a decision that they later come to regret [12,29]. In addition, clinician judgement has been shown to be poor at predicting when patients will die.[23]

An expert panel convened by the European Intensive Care Society, the American Thoracic Society, and the Society for Critical Care Medicine has identified late deaths after critical illness as a priority research area.[18]

Realistic 80 is the largest trial of critically ill elderly patients to date. Strengths of this dataset include the richness of pre-morbid patient data, its prospective nature, the heterogeneous patient population, and the inclusion of a large number of teaching and non-teaching centers.

There is abundant evidence that ICU mortality worsens with increasing age, [11,18,20,25,28,29,34] and this is also intuitively obvious. It has also been repeatedly demonstrated that elderly ICU patients can have very good outcomes.[12,13,16-20] While our data demonstrate a statistically significant difference in age between survivors and non-survivors, the six month difference does not seem clinically meaningful.

As expected, the Apache II and Charleson comorbidity scores were higher in non-survivors than survivors. Surprisingly, the functional comorbidity indices were similar between the two groups. This contrasts a recent publication showing an association between premorbid frailty and hospital (although not ICU) survival.[21]

SOFA scores were similar between medical patients (5.3+/-3.4) and surgical emergency patients (5.4+/-3.3) on the first day of ICU stay. Despite similar organ dysfunction scores upon ICU admission, very old critically ill medical patients had longer ICU stays, but shorter hospital stays, than their surgical emergency counterparts.

Less than half of the patients who survived to hospital discharge were able to go home (45% of the medical patients and 41% of surgical patients). A significant fraction of the patients (46% of medical patients and 51.4% of surgical patients) who were discharged from their admitting hospital within 1 year of admission were ultimately transferred to either another hospital, or to a long term care facility.

We believe that our data on ICU survival, hospital survival, and eventual location of hospital discharge, combined with the mean lengths of stay, will help inform decision makers **at the time of consideration for, or ideally prior to, ICU admission**.

We acknowledge that even the most robust data are not a substitute for a compassionate, patient centered, end-of-life discussion with patients and / or their substitute decision makers. We expect that this information will compliment high quality end-of-life meetings, thereby allowing surrogate decision makers to make more informed, patient focused end-of-life decisions.

Although this study enrolled a large number of very old critically ill patients across 22 different centers, it still suffers from several important limitations. In particular, the following factors limit the generalizability of this study's findings.

This study enrolled only patients who were actually admitted to ICUs, thereby systematically excluding all elderly patients who died at home, who were not transferred to hospital from their nursing homes, and those with previously expressed wishes not to be admitted to ICU or placed on life sustaining therapies. There were likely many critically ill elderly patients who were referred to ICU, but who were refused admission because their prognosis was felt to be too poor, or because during a pre-ICU admission family meeting, it was decided not to admit the patient to ICU.

Patients who survived their ICU admission, were transferred to the ward, and were subsequently transferred out of the study hospital were assumed to have survived their hospital stay. This is a significant limitation of our data, one that affected 288 (26.5%) out of the total 1671 patients in the study.

Unfortunately, we did not collect outcome data on patients referred to ICU, but not admitted. It is for these reasons that our results are biased towards overly optimistic outcomes, and may explain why the ICU and hospital mortalities of the study patients do not differ significantly from those of younger ICU patients with similar degrees of illness.[35-38]

In general, the published ICU survival rates in very elderly patients are extremely variable, likely reflecting differences in inclusion criteria and / or patient type (medical versus surgical emergency versus elective surgical).[17,24] For the purposes of our future clinical prediction rule derivation, erring on the side of survival optimism seems preferable.

This study enrolled a very low cohort of critically ill elderly trauma patients, another patient population for which there are not a lot of long term outcome data.

Withdrawal of life support occurs earlier in the clinical course of very old patients who are not showing clinical improvement.[22] The decision to withdraw life sustaining therapies on a futility basis relatively early in the ICU course biases our data, shortening the expected lengths of stay, though not necessarily affecting overall mortality. This bias could potentially make the length of stay data appear falsely optimistic to decision makers.

Some of the previously discussed factors limit the generalizability of our findings to patients who are transferred to hospital, and referred for ICU admission. It is our vision to produce data that can inform advance care planning in the healthy elderly outpatient population. Ideally, this planning could occur with family members and patients' general practitioners in a non-acute setting. Our results are still valuable for serving such a function, but must be interpreted within the previously stipulated contexts.

In addition to informing decision makers about ICU and hospital mortality, our data also provide practical data on median ICU length of stay, hospital length of stay, and the fraction of critically ill elderly patients who are able to return home post critical illness.

Future papers will produce **more individualized** predictions of likely patient outcomes in the form of clinical prediction tools. These tools will use data from patients' pre-morbid medical status, and their physical examination and laboratory tests **obtained prior to ICU admission** to predict low, moderate, or high probability of hospital mortality and / or functional outcomes. Once prospectively validated, these individualized prediction tools will provide much more useful information to decision makers than mean cohort data.

An intervention study targeted at improving concordance between patient / family expressed wishes and ICU interventions by using data from this study would be the basis for a future impact study based on the current work. A health economic analysis could be performed independently or in concert with the previously mentioned impact evaluation.

Conclusions

Realistic 80 is the largest dataset to have evaluated the experiences of critically ill, very old patients. As stand-alone data, our results can inform end-of-life decision making, not only regarding ICU and hospital mortality, but more practical outcomes as well, such as length of stay, and location of eventual hospital discharge.

Chapter 4 -- Comments on Manuscript 1

Manuscript 1 was very useful in its ability to describe the Realistic 80 patient population, and to provide general estimates of their mean ICU and hospital lengths of stay, their mortality, and their chances of returning home. While the values will not be individualized, they can nonetheless inform family decision making and are an improvement on the current practice of physicians making a "best guess" on patient prognosis without the benefit of any supporting data.

The limitations discussed in manuscript 1 are important ones.

Namely, the mortality is very low. The reasons for the low mortality were articulated in the manuscript, so they won't be repeated here. This should be presented to families as a "best case scenario". The same strategy could be used when applying the data from manuscript 1 to the chances that patients are able to return to independent living.

The converse situation may apply for ICU length of stay. There is evidence that elderly patients' families tend to withdraw life sustaining therapies earlier than those of younger patients. This phenomenon may bias the ICU length of stays toward the appearance of being falsely shorter than the reality, when patients stay for the whole course of ICU care.

Perhaps the most serious limitation with the Realistic 80 dataset is the loss to follow up of 26.5% of all the study participants. These were patients who survived their index ICU stays, were transferred to the ward of their admitting hospitals, and were subsequently transferred to other, non-study hospital wards. The study did not have adequate funding to follow these patients once they left the study hospital. Considering these patients to be survivors and to have left hospital biases estimates of hospital length of stay, and mortality. It will not affect estimates of ICU lengths of stay, or ICU mortality.

Chapter 5 -- Introduction to Manuscript 2

Manuscript 2 describes the first of the two clinical prediction rules. The rule was derived from the Realistic 80 dataset. It is the nature of clinical research that sometimes factors beyond the investigators' control affect the collection of data. Indeed, there were several such challenges in this study.

The study ran short of funding prior to completion, so some centers had eligible patients that they were unable to enroll.

The second challenge was that the manner in which data was recorded and reported was not consistent across centers. Both of these events have affected the prediction tool derivation and will be discussed both within the manuscript, as well as in more detail in Chapter 7 of this thesis.

The largest limitation of the Realistic 80 dataset to the prediction tool derivation was the lack of follow up for study participants who were transferred to non-study hospitals. We assigned patients who were transferred to non-study hospitals as survivors for the purposes of the prediction tool derivation. In the discussion section of the manuscript we acknowledge that this will contribute to an optimism bias for our clinical prediction tool.

Chapter 6 -- Manuscript 2

A Clinical Prediction Rule for Hospital Mortality in Critically Ill Elderly Medical Patients

Abstract

Background: Very elderly (80 years of age and above) critically ill patients admitted to Medical ICUs have a high incidence of mortality, prolonged hospital length of stay, and living in a dependent state should they survive.

Objective: To improve future end-of-life decision making for very elderly patients admitted to Canadian ICUs by deriving a clinical prediction tool for hospital mortality.

Methods: Data from Realistic 80 (a prospective, multicenter cohort study of very elderly medical patients admitted to 22 Canadian academic and non-academic ICUs) was used. A univariate analysis of selected predictors to ascertain prognostic power was performed, followed by bidirectional stepwise multivariable logistic regression to derive the final prediction tool.

Results: A total of 1033 elderly patients met study inclusion criteria. The mean age was 84.6, with a standard deviation of 3.5 and a range of 79.9-100.2. The participants were 55% male. The baseline Apache II score was 23.1; SOFA was 5.3. ICU mortality was 26.5% and hospital mortality was 41.5%. Important predictors of hospital mortality at the time of ICU referral include: age [85-90 years of age had an odds ratio of hospital mortality of 1.63 (1.04-2.56), >90 years of age had an odds ratio of hospital mortality of 2.64 (1.27-5.48)], serum creatinine [120-300 had an odds ratio of hospital mortality of 1.57 (1.01-2.44), >300 had an odds ratio of hospital mortality of 5.29 (2.43-11.51)], GCS [13-14 had an odds ratio of hospital mortality of 2.09 (1.09-3.98), 8-12 had an odds ratio of hospital mortality of 2.31 (1.34-3.97), 4-7 had an odds ratio of hospital

mortality of 5.75 (3.02-10.95), 3 had an odds ratio of hospital mortality of 8.97 (3.70-21.74)], and serum pH [<7.15 had an odds ratio of hospital mortality of 2.44 (1.07-5.60)].

Conclusion: The use of a simple mortality prediction tool, based on data that is easily available at the time of ICU referral, can inform decision making regarding end of life care. The use of a robust clinical prediction tool will compliment clinician judgment, enhance confidence in end-of-life decision making, optimize the alignment between goals of care and realistic clinical outcomes, and improve health care resource utilization. Our model's performance is very good, and will serve to inform clinical practice once validated.

Keywords: Intensive care unit, elderly, prediction rule, decision rule, prognosis, survival, end of life care.

Manuscript

The eldest sector of the population is growing faster than all other age groups, both around the world, and in Canada.[2,3] In 1931, less than 60% of males and 62% of females survived to age 65, compared with 84% and 90% respectively, in 2001. The main causes of death in this demographic group are degenerative diseases and cancer [5]. Twenty percent of these deaths occur in Canadian Intensive Care Units. [6,7] Patients over the age of 65 currently account for half of ICU admissions and nearly 60% of all ICU days. [8-10] This large change in our demographics, combined with a consistently increasing population, is putting tremendous strain on our health care system in general, and on critical care resources specifically. There is conflicting evidence regarding whether or not ICU mortality worsens with increasing age.[11,20,28,29,34,39] It has been repeatedly demonstrated that elderly ICU patients can have very good outcomes.[35-38]

Based on survey data from both Canada and abroad, most people would prefer to be cared for and to die in their own homes.[7-9] In addition, although 70% of elderly patients state a preference for comfort care over high technology life prolonging treatment in an inpatient setting, 54% are still admitted to intensive care units.[10-11] More concerning was the fact that 57% of respondents stated that they would decline a subsequent life sustaining ICU admission in the event of a recurrent critical illness.[29] A 2006 study by Heyland et al.[12] identified that elderly Canadians value quality, not quantity of life, and do not want technology supported life prolonging measures. Canadian Intensive Care Units continue to mechanically ventilate and use life prolonging technology in the elderly, even when there is little chance of meaningful recovery. There is currently a significant disconnect between the wishes of the Canadian population and the ground level clinical practice. This discrepancy disrespects patient autonomy, and prolongs the dying process at significant expense to the health care system.

Our primary objective was to derive a clinical prediction tool to inform decision making at the time of ICU referral. Our prediction rule for hospital mortality in critically ill elderly patients is derived from the largest prospective dataset to date in this population. We used both academic and community ICUs and have evaluated its performance by internal validation.

The use of a robust clinical prediction tool can complement clinician judgment, enhance confidence in end-of-life decision making, optimize the alignment between goals of care and realistic clinical outcomes, and improve health care resource utilization.

Methods

Design and Setting

This is a secondary analysis of the REALISTIC-80 Study (Realities, Expectations and Attitudes to Life Support Technologies in Intensive Care for Octogenarians), clinicaltrials.gov NCT01293708,a multicenter, prospective, observational cohort study conducted from September 2009 to February 2013. Twenty two Canadian academic and community ICUs participated. Waived consent was obtained from each local Research Ethics Board. All patients over eighty years old who were admitted to ICU were eligible.

Study Population

We included a consecutive sample of all patients admitted to participating ICUs who were 80 years of age or older. Enrollment began in September 2009, and was completed in February, 2013. Although data was gathered on medical, surgical emergency, and elective surgical patients, this paper will focus exclusively on the medical patients. Previously enrolled patients who were re-admitted to the ICU were not re-enrolled, as comprehensive data collection continued for 12 months following the index ICU admission. Routine local practices regarding criteria for ICU admission

were maintained.

Baseline Data Collection

Trained research personnel collected data on the following outcomes for each study participant: age, sex, marital status, living status, APACHE II, [26] SOFA, [31] Functional Comorbidity Index, [32] Charlson Comorbidity Index, [33] admission type (medical, surgical emergency, surgical elective), following acute or chronic illness, length of hospital stay prior to ICU admission, primary ICU diagnosis, number of hospitalizations and emergency department visits in the preceding 12 months, serum albumin, body mass index, number of days in ICU, number of days in hospital, number of days of mechanical ventilation, vasoactive medication use, renal replacement therapy, and survival.

Survival was defined as being discharged from hospital, or alive in hospital one year post ICU admission. Early in the recruitment phase, funding allowed for each site to enroll a convenience sample of the first 60 eligible patients. Partway through the study, this number was decreased to 30 patients per site.

Data Analysis

Continuous variables were described by means, standard deviations, and ranges, with the exception of length of stay variables which were described by medians, quartiles, and ranges because of their positive skews. Categorical variables were described by counts and percentages. The association between predictors and the primary outcome was evaluated by univariable logistic regression. Continuous variables were categorized using the most discriminative cutpoints. Predictors with association P values < 0.2, that were deemed practical for routine emergency department of ward use and availability, and were felt to have high inter observer reliability were included in the multivariable logistic regression model. Interobserver reliability was not formally assessed in this derivation phase

Univariable analysis was used to evaluate the associations between predictor variables and the primary outcome (all cause hospital mortality). Continuous variables were categorized based on discriminative ability, and clinical sensibility. For example, age was categorized into five year intervals between 80 and 90, and then > 90 because of the smaller n in that group. Statistical techniques for categorizing continuous variables are available[40], but the use of practical cutpoints with strong discriminative capacity may be preferable. Multivariable stepwise bidirectional logistic regression was performed using the predictors that were identified on univariable analysis as being associated with mortality ($p<0.2$), and felt to be widely available in most emergency departments or hospital wards (the usual ICU entry points for critically ill medical patients).

The preliminary mortality risk stratification scale consists of simple elements that are easily available in emergency departments and hospital wards. Historical elements may be available from the patient, their chart, or their substitute decision maker. Clinical elements are obtained during patient examination. Metabolic elements are derived from simple blood tests. The risk scale used in this analysis was created by exponentiating the beta coefficients from the logistic regression model, then dividing all of the beta coefficients by the lowest beta coefficient value, and rounding the resultant values to the nearest whole number. In this manner, a relative risk scale was created.[41,42]

SAS version 9.3 (SAS Institute, Cary, N.C., USA) was used for the statistical tests.

Results

There were 1033 patients included in this study, with none missed, and no patients were lost while in the study hospitals. This high recruitment and follow up rates were due to the waived consent that was granted by each local Research Ethics Board (data could be extracted from the patient chart by research personnel, even after a patient death). All patients admitted to participating study sites during the

enrollment period were included. (Figure 1) Due to the ICU and hospital based nature of this study, there were no losses to follow up.

The mean study patient age was 84.6, with a standard deviation of 3.5 and a range of 79.9-100.2. The participants were 55% male. They had significant illness acuity (mean Apache II 23.1). Over half of them had a respiratory or cardiovascular diagnosis. Sepsis, neurologic, and gastrointestinal medical illnesses comprised the bulk of the remaining participants (Table 4). Interestingly, patients worsened after their first ICU day (Mean Delta SOFA 0.8).

The median index ICU length of stay was 4.0 (IQR 5.9) days. Over a quarter (26.5%) of patients did not survive to ICU discharge. Only a small proportion (5.7%) of all study participants were readmitted to the ICU if they survived their index admission (Table 5). The median index hospital length of stay was 16.2 (IQR 25.0) days. Hospital mortality (including those patients who died in the ICU) was 41.5%. Patients were considered survivors if they were still alive one year after their admission. Of the survivors, less than half (45%) were able to return home. Nearly a quarter (22.5%) of survivors required transfer to long-term care facilities. Another quarter of survivors (24.7%) were transferred to wards in other hospitals. Unfortunately, these patients were lost to further follow up and so were considered to have been discharged alive from hospital. Taking the worst case scenario approach (that all of these patients died soon after hospital transfer), would increase the hospital mortality from 41.5% to 69.5%. (Table 5)

Univariable Data Analysis

A univariable logistic regression analysis was performed using 13 of the Apache II components as the independent predictors and hospital mortality as the dependent variable. Gender, serum sodium, serum potassium and white blood cell count high were excluded on the basis of their P values of >0.05. (Table 6) White blood cell low was excluded from the multivariable analysis because of the low number of values. The respiratory rate values did not account for whether or not patients received mechanical

(invasive or non-invasive) ventilation. For this reason, respiratory rate was excluded from further analysis because the sickest patients would have been mechanically ventilated, thereby normalizing their respiratory rates.

Multivariable Data Analyses

The multivariable logistic regression model was developed using 436 (42.2%) of the 1033 patients that were enrolled in the trial. (Figure 1). The reason for this large loss of cases will be discussed in a subsequent section. Seven of the thirteen predictor variables from the univariable analysis were evaluated by bidirectional stepwise multivariable logistic regression. Four of the seven were statistically significant and will comprise the Preliminary Risk Scale. Participants over 85 years of age had a mortality odds ratio of 1.63 with respect to their 80-84 year old counterparts. Patients over 90 years of age had an odds ratio of 2.64. Kidney function was a very discriminative mortality predictor. Patients with serum creatinine levels of 120-300 had a mortality odds ratio of 1.57. Those with serum creatinine levels over 300 had a mortality odds ratio of 5.29. Level of consciousness (as measured by GCS) showed a consistent increase in mortality across the categories. Serum pH was dichotomized to above and below 7.15. Patients with acidemia on arrival to the ICU had a mortality odds ratio of 2.44 with respect to their less acidemic counterparts (Table 7).

The Hosmer-Lemeshow chi-squared goodness-of-fit statistic was non-significant ($p=0.6$) which suggests a good fit to the data. The area under the receiver operating curve was 0.72 (0.67-0.77), meaning that the model correctly classified 74% of cases for survival or mortality.

Preliminary risk scale

Our preliminary ICU mortality prediction tool consists of four predictors: age, kidney function, level of alertness, and pH. The highest possible score is 13. (Table 8) A strength of the risk scale is its simplicity and the widespread and rapid availability of all its components. Some precision was lost by rounding the beta coefficients from the regression analysis, but we feel this is an acceptable concession for ease of use.

We found that the risk of hospital mortality ranged from 18.5% for a score of 0, to 96.8% for a total score of 12. (Table 9) It is noteworthy that no patients within the study had a risk score of 13.

The classification performance of our Preliminary Risk Scale is shown in Table 10. For each risk score, the number of study participants with each value, the scale's estimated probability of death, and the sensitivity and specificity of the prediction is shown. The sensitivity and specificity values for the probability of death are based on the risk score on Day 1 of ICU admission.

The classification performance of the final score categories was validated across 1000 replications with the bootstrap method.[43] (Table 11) The c statistic was 0.72 (95% CI 0.72, 0.72), evidence of acceptable accuracy.

Discussion

Among the critically ill elderly patients in this cohort, we observed a significant hospital mortality that increased proportionally to their Preliminary Risk Scale Score. We identified that a small number of readily available predictors are strongly associated with hospital mortality: patient age, Glasgow Coma Score, renal function, and serum pH. These high risk factors do not require sophisticated testing, advanced imaging or invasive procedures.

The classification performance of the Preliminary Risk Scale is very good at the high and low scores, respectively (Figure 2). Between scores of 2-5, the classification performance worsens. Clinically, this seems acceptable as it is less likely that substitute decision makers will make decisions regarding direction of care when estimated mortality is within this mid-range.

Use of this scale in both the high and low ends of the range, where it is both more accurate, and predicts either a very good or a very bad outcome, could

significantly improve decision making for patients' families. Confirmation that the estimated mortality is in the middle range may still be reassuring and enlightening for clinicians and substitute decision makers alike.

How this Compliments the Literature

In some European countries, patients are already being refused ICU access on the basis of advanced age alone.[41] The Canadian Critical Care Research Network (CCCRNET) database of over 200 000 ICU admissions demonstrates an increase in the proportion of octogenarian admissions from 10% in 1994 to 14% in 2005.[34] An Ontario critical care database demonstrated that from 2006-2008, octogenarians comprised 18% of ICU admissions.[28] Ontario hospital ICU mortality data from 2001-2003 showed that one year after hospitalization, 48% of critically ill octogenarians had died, compared to a 23% ICU mortality in patients under 80 years of age.[20] In a single center, French study published in 2006, 180 critically ill octogenarians were followed to one year post hospital discharge. The hospital and 1 year mortality rates were 63% and 71%. Survivors described higher rates of depression, isolation, and lower mobility than an age and sex matched community cohort.

Clinical Implications

Our clinical prediction tool is intended to inform decision makers **at the time of ICU admission** regarding likely outcomes for critically ill elderly patients**.** In addition to providing an estimate of hospital mortality should maximal life support be instituted, the data from this trial will allow clinicians to educate decision makers regarding duration of ICU and hospital admission. Lastly, decision makers may be educated about the mean number of study patients who were able to return to independent living. The simplicity of the rule should improve its acceptance and implementation by clinicians, as emphasized in a previous similar study.[44] Any prediction rule that will be used to inform decisions regarding withholding or withdrawal of life sustaining therapy must demonstrate high specificity. This importance has been stressed in previous similar studies.[44]

Although the powerful predictive properties of a relatively small number of Apache II components has been demonstrated, the numerical values in this Risk Scale should not be used clinically until they have been externally validated. It does seem reasonable at this time for clinicians to use the mean survivorship data, and the components of the Risk Scale in clinical practice.

Study Strengths

Strengths of this study include the large number of participants, the large number of recruiting ICUs, and its prospective nature. Our clinical prediction rule has been derived from the largest prospective trial ever completed on critically ill octogenarians. It has shown very good predictive ability when internally validated via bootstrapping. This prediction rule does not require the presence of an accurate diagnosis, nor does it require any kind of neurologic evaluation beyond the well validated Glasgow Coma Score.[45] The risk scale is easy to remember, objective, and practical. As previously mentioned, when validated internally on 1000 bootstrap samples, the model performed very well, particularly at the high and low ends of expected hospital mortality.

Study Limitations

The Realistic 80 data used to derive the Preliminary Risk Tool were gathered on the first day of patients' ICU admission. Applying these data to a decision rule for use *prior to* ICU admission is imperfect. In most cases, the data are likely to be consistent with pre-admission values.

There was a great deal of missing data. This was due to the fact that participating centers were given the option of reporting either an aggregate Apache 2 score, or individual values. It turned out that nearly half of centers chose to report aggregate scores, and half reported the component data. It is our belief that this data should be considered missing completely at random. The ratio of predictors to events was still large enough to derive a meaningful Risk Tool. Tables describing the included and not included patients are available in the appendix.

Patients in the study who were transferred from the study hospital to another hospital were considered to have survived their hospital stay, because we were unable to follow their trajectories post transfer. This practice may have introduced some error as patients who died after transfer would be considered survivors and would bias our Risk Tool towards being overly optimistic.

Another study limitation stems from the fact that we only enrolled patients who were transferred to hospital and subsequently referred to and accepted by an ICU. This enrollment bias also contributed to an overly optimistic Risk Tool. All sick elderly patients who declined transfer to hospital (those that died at home, in nursing homes and hospices), whose physicians deemed them unsuitable for ICU (pre or post ICU referral), and those who were refused ICU admission on any grounds, would not have qualified as potential study participants.

Despite these limitations, we believe that the ability to provide decision makers with some objective, robustly derived data to educate them regarding mortality estimates, and ICU and hospital admission duration, is a significant advance for improving informed decision making.

Research Implications

We are pleased by the simplicity of our Preliminary Risk Scale, and its performance on the 1000 bootstrap samples. There was a strong correlation (particularly at the high and low ends of mortality) between our Risk Scale's mortality predictions and the observed values in our sample.

The next step in our research is to assess our Risk Scale's performance in an external sample taken from different institutions. No clinical prediction tool is ready for clinical implementation until it has undergone external validation. Future steps include an implementation phase to demonstrate the impact and penetration of the rule into routine clinical practice, an economic analysis to evaluate the financial implications of rule implementation, and a dissemination phase that includes strategies for

knowledge translation to relevant audiences.

Conclusions

Critical care physicians are frequently asked by the families of critically ill elderly patients to help with end of life decision making. Implicit in these discussions are details regarding prognosis, survival chances, and eventual functional status. We have identified high risk characteristics for hospital mortality in the elderly population and developed a unique risk scale that can be used to inform goals of care and end of life meetings prior to implementation of the institution of life support. Once externally validated, this scale will benefit critically ill elderly patients, their families, and health care systems by improving end of life decision making.

Chapter 7 -- Medical Patient Prediction Rule Derivation Sequence and Justification

Patients were enrolled at 22 participating Canadian sites between September 2009 and February 2013. The following data were collected:
Age, gender, marital status, living status, Apache II score, SOFA score, admission type (medical versus surgical emergency versus elective surgical), admission following acute or chronic illness, length of hospital stay prior to ICU admission, primary ICU diagnosis, comorbidities, number of hospitalizations and ED visits in the preceding 12 months, serum albumin, BMI, number of ICU days, number of hospital days, number of days of mechanical ventilation, survival.

Decision to Exclude Elective Surgery Patients

In discussion with members of my thesis committee, it was decided not to analyze the elective surgery patients. There were two main reasons for this. First and foremost, the elective surgery patients are a very different population than the other two. It seemed unreasonable to combine them with the rest of the cohort, or even with the surgical emergency patients. Most of the elective surgery patients underwent either cardiac or vascular surgery. Generally, for surgeons to be willing to perform elective surgery on patients over 80 years of age, they need to be quite healthy, independent and high functioning.

Secondly, the goal of our prediction rule is to inform decision making regarding goals of care for critically ill patients. Not only are these elective surgery patients too healthy, but the decision making process about goals of care is generally handled in the surgeon's office preoperatively. It is not a discussion between the substitute decision maker and the ICU team / emergency department team / or ward medical team.

Decision to Analyze Medical and Surgical Emergency Patients Independently

In discussion with my thesis advisory committee, and after posing this question to the Canadian Critical Care Trials Group at their June 2013 spring meeting, it was decided to analyze the medical and surgical emergency patients separately. Intuitively,

they are distinct patient populations, and our own data support this. Their ICU lengths of stay, hospital lengths of stay, ICU mortality, hospital mortality, and likelihood of returning to independent living are all different (Table 3 from Manuscript 1).

It followed that if the medical and surgical emergency patients were to be analyzed separately, then we would derive independent prediction rules, and write two separate manuscripts.

Univariable Analysis

Table 6 shows the association between patient variables (available at the time of ICU admission) and all cause hospital mortality. Table 6 was the univariate analysis that was performed after the data were cleaned. "Cleaning" involved reviewing all of the raw data and evaluating every value that seemed implausible. For the most part, there were few errors in the data, and little cleaning was required. The initial univariate analysis was performed on the entire cohort of medical and surgical emergency patients together. It has been included in the appendix of this thesis, but will not form part of the manuscript that is submitted for publication. (Appendix Table 1)

Some continuous variables were further categorized using cutpoints that were selected on clinical and practical grounds. This stage of the analysis was performed separately for the medical and surgical emergency groups. An example of this analysis (for the medical patients) is also shown in Table 2 of the appendix, but will not form part of the manuscript.

Interaction Terms

In cases where a prediction model has covariates (ex. X_1 and X_2) whose effects cannot be separated, it is necessary that the analyst creates an interaction term (usually X_1X_2), adds it to the regression model and evaluates whether or not the interaction term has a significant association with the dependent variable. When interaction terms are introduced into a model, the effects of the individual covariates of the interaction term cannot be reliably measured. When interaction terms turn out to be more

important predictors than their component covariates, the interaction terms should remain in the final model.

Previous similarly derived prediction tools have described an assessment for "clinically sensible interaction terms", but have not included any in the final model.[42] From a purely methodologic perspective, every potential interaction term should be assessed and included in the model where appropriate. However, when designing a tool for clinical use, ease of recall and simplicity become important considerations.[44] In this model, we did not test for interaction terms for two reasons. The first is that there are no strong clinical reasons for any of the predictors in our model to have a particularly important effect on any other. The second reason is that we don't want to limit the clinical utility of the final model by including complex interaction terms.

Transformations

In some models, higher powers of predictor variables can be included in the model to better approximate non-linear associations. Polynomials can have good fits for some values (with continuous outcomes), but may also perform poorly for others. They are much less useful for "threshold effects" and / or binary outcomes.[46,47] As per recent similar clinical prediction rule publications[48,49], no transformations of the predictor variables were performed.

Medical Patients – Univariate Analysis

Continuous variables were "cut" into categorical ones. The thresholds for where to divide the categories were based on practicality and medical sensibility. The decision of whether or not to categorize continuous predictors is controversial.[46,50,51] It is generally felt to be "unwise to categorize naturally continuous variables during data collection, as the original values can then not be recovered, and if another researcher feels that the (arbitrary) cutoff values were incorrect, other cutoffs cannot be substituted".[46] We collected the data as continuous, but then categorized it in order to eventually be able to allocate each category in the final model a "point assignment" for the risk scale. This approach has been successfully used with previous prediction rules [42,43,48,49] several of which are from the University of Ottawa.

In addition, with several of the predictors, categories were collapsed to form larger categories, and cut points were adjusted and the regression repeated. In discussion with Dr. Stiell, it was acknowledged that this practice feels like "massaging the data", but this is an acceptable approach during the *derivation* phase.

At this point, variables from the univariate analysis were included in the multivariate analysis if the following conditions were met: univariate regression P value<0.2, adequate numbers of patients within the category, and a reasonable chance that this data would be available in most emergency departments or hospital wards at the time of a goals of care discussion prior to ICU admission. Variables were excluded from the multivariable model if their values would be affected by patient care processes (ex. respiratory rate is affected by sedation and mechanical ventilation and was therefore excluded).

Management of Missing Values

Approximately half of the enrolled patients had missing data. Essentially all of the missing data was due to the fact that the study protocol allowed sites to choose whether to record an aggregate Apache II score, or its individual components. In addition, sites were not required to choose one of the two options and then be consistent with all of the patients that they enrolled. Out of the 22 sites, 20 reported individual components and 16 reported aggregate scores. Much of our prediction score was comprised of Apache II score components. In the ICU setting, there is ample time for obtaining data, and the nature of the R 80 data allowed it to be gleaned from the patient chart at a later time if it was missed by research personnel on the first pass. Other than the Apache II components that were missing (all of the components were missing) in half of the medical and half of the surgical patients, there was no other missing data that needed to be managed.

In general, the cause of missing data must be evaluated and subsequently classified as: missing completely at random (MCAR), missing at random (MAR), or informative missing (IM). Imputation techniques are available to salvage subjects for study inclusion rather than excluding them from an analysis altogether. For the

Realistic 80 data, most of the predictor variables were continuous and unrelated to each other, in which case single conditional imputation (whereby mean or median values are substituted for the missing predictor value) is appropriate.[46] In cases where the covariate's missing data is related to other data, more sophisticated imputation techniques that use a predictive model that is based on the other data are more appropriate.[46]

Multiple imputation involves taking random samples from the "distribution of the target variable given the other variables".[46] Formulas used to calculate standard errors must take into account the incomplete data and the use of multiple imputation or they will yield incorrect results.[50] Further detail is beyond the scope of this thesis.

Fortunately, it is felt that the missing data in our particular case are truly missing completely at random. In addition, there is so much missing data for the affected patients, that they require exclusion from the study altogether. Unfortunately, this did significantly reduce our sample size and affect our ability to effectively derive a meaningful prediction tool for the emergency surgery population.

Model Validation

The purpose of model validation is to determine how effectively a newly constructed model can predict responses on either future subjects, or on subjects that were not part of the derivation cohort.[46] Validation can be external or internal.

External Validation

External validation is the preferred method and increases confidence in the generalizability of a prediction tool. In its purest form, external validation is performed prospectively, on a new patient population, in a different country. In this manner, the ability of the data collection instrument to perform in a different language and a different culture is assessed.

For the purposes of Realistic 80, we hope to eventually externally validate our rule in Canadian hospitals, including some that did not participate in the derivation phase. This would be a modified version of the second purest form of external validation: a prospective validation in a similar geographic area, but at a different institution than that of the derivation phase.

The third, and least desirable form of external validation involves using a portion of the original dataset for derivation, and setting aside a predetermined number of participants for the validation phase. This is also known as data-splitting. In cases where a chronological split is used, the validation can be described as prospective.

Bootstrapping has been shown to be as effective as data-splitting on a sample twice as large.[50]

Internal Validation

Bootstrapping is a method for internally validating a prediction rule. It is commonly used in clinical prediction research. When performing this technique, one uses simulation to evaluate the accuracy of a prediction rule on a sample taken from the original dataset. This process is repeated many times (often several hundred times) with randomly selected internal samples each time. Mean and median statistics of interest from the samples can be computed and compared to the values predicted by the model. Use of Efron's bootstrap does not require knowledge of the distribution of the data.[46]

For predictive models derived from large datasets, the fraction of original data

points that are selected for each bootstrap sample is $1-e^{-1}=0.632$.[46]

The concern with ordinary bootstrapping is overfitting of the model, as the predicted accuracy is artificially improved by the very nature of an uncorrected, internal validation. More sophisticated bootstrap models have been developed that attempt to estimate the overfitting optimism and correcting for it.[43,50-54]

Overfitting secondary to bootstrapping has been shown to be worse when the ratio of number of patients to number of predictors is small.[46] Additionally, in simulations using binary logistic regression models (such as the Realistic 80 model), the original bootstrap technique has been shown to have lower mean squared error than corrected models, as long as n is greater than 200.[55] Since this was the case in both the medical patients and the surgical emergency patients, we selected Efron's original bootstrap for internal validation.

We do recognize that although this is an effective form of internal validation, our model will not be ready for clinical application until validated in a prospective, external population.

Model Parameter Interpretation

In a linear regression model, the beta coefficients of the predictors are easily interpretable i.e. the beta coefficient represents the change in the property of the outcome variable per one unit change in itself. In a binary logistic regression model, such as the one we used, the beta coefficients represent the change in log odds of the outcome variable per unit change. Left in this format, these beta coefficients are difficult to interpret clinically.

The risk scale [42] used in this analysis was created by exponentiating the beta coefficients from the logistic regression model, then dividing all of the beta coefficients by the lowest beta coefficient value, and rounding the resultant values to the nearest whole number. In this manner, a relative risk scale was created.

Risk Score Internal Validation

The classification performance of the risk scale should be calculated. As previously mentioned, internal validation via the bootstrapping technique can assess the sensitivity, specificity, positive and negative likelihood ratios of the derived risk scale, when it is applied to many randomly drawn replicate samples *from within the original sample.* Internal validation of the risk scale for this Master's thesis was performed by the bootstrapping method. To reiterate, even after satisfactory internal validation, clinical prediction tools should not be used clinically until prospectively validated on an external sample.

Chapter 8 -- Introduction to Manuscript 3

Manuscript 3 describes the derivation of the second of the two clinical prediction rules. Similarly to the prediction tool for medical patients, this rule was also derived from the Realistic 80 dataset.

As mentioned during the discussion of Manuscript 1, it is the nature of clinical research that sometimes factors beyond the investigators' control affect the collection of data. Indeed, there were several such challenges in this study.

The study ran short of funding prior to completion, so some centers had eligible patients that they were unable to enroll.

The second challenge was that the manner in which data was recorded and reported was not consistent across centers. Both of these events have affected the prediction tool derivation by significantly reducing the number of patients enrolled in the trial as well as causing missing data. These issues will be discussed both within the manuscript, as well as in more detail in a future chapter of this thesis.

Chapter 9 -- Manuscript 3

A Clinical Prediction Rule for Hospital Mortality in Critically Ill Elderly Surgical Emergency Patients

Abstract

Background: Very elderly (80 years of age and above) critically ill patients admitted to Surgical ICUs have a high incidence of mortality, prolonged hospital length of stay, and living in a dependent state should they survive.

Objective: To improve future end-of-life decision making for very elderly patients admitted to Canadian ICUs by deriving a clinical prediction tool for hospital mortality.

Methods: Data from Realistic 80 (a prospective, multicenter cohort study of very elderly surgical patients admitted to 22 Canadian academic and non-academic ICUs) were used. A univariate analysis of selected predictors to ascertain prognostic power was performed, followed by multivariable logistic regression to derive the final prediction tool.

Results: A total of 418 elderly patients met study inclusion criteria. The mean age was 84.4, with a standard deviation of 3.4 and a range of 80.0-96.6. The participants were 53.6% male. The baseline Apache II score was 22.1; SOFA was 5.4. ICU mortality was 18.7% and hospital mortality (ICU + ward mortality) was 31.6%. Important predictors of hospital mortality at the time of ICU referral include: serum creatinine [120-300 had an odds ratio of hospital mortality of 2.83 (1.41-5.68), >300 had an odds ratio of hospital mortality of 16.33 (2.5-106.24)], and serum pH <7.15 had an odds ratio of hospital mortality of 6.0 (1.34-26.85)]. Study participants with a risk score of 0 had a 20% mortality, those with a risk score of 1 had a 46.3% mortality, those with a risk score of 2 had a 100% mortality, and those with a risk score of 3 had a 62.5% mortality.

Conclusion: The use of a simple mortality prediction tool, based on data that are easily available at the time of ICU referral, can inform decision making regarding end of life care. The use of a robust clinical prediction tool will compliment clinician judgment, enhance confidence in end-of-life decision making, optimize the alignment between goals of care and realistic clinical outcomes, and improve health care resource utilization. The model's performance is promising, but can be strengthened by incorporating additional data in a subsequent phase.

Keywords: Intensive care unit, elderly, prediction rule, decision rule, prognosis, survival, end of life care.

Manuscript

The eldest sector of the population is growing faster than all other age groups, both around the world, and in Canada.[2,3] In 1931, less than 60% of males and 62% of females survived to age 65, compared with 84% and 90% respectively, in 2001. The main causes of death in this demographic group are degenerative diseases and cancer.[5] Twenty percent of these deaths occur in Canadian Intensive Care Units.[6,7] Patients over the age of 65 currently account for half of ICU admissions and nearly 60% of all ICU days.[8-10] This large change in our demographics, combined with a consistently increasing population, is putting tremendous strain on our health care system in general, and on critical care resources specifically. There is conflicting evidence regarding whether or not ICU mortality worsens with increasing age.[11,20,28,29,34,39] It has been repeatedly demonstrated that elderly ICU patients can have very good outcomes.[35,36,56-58]

Based on survey data from both Canada and abroad, most people would prefer to be cared for and to die in their own homes.[7-9] In addition, although 70% of elderly patients state a preference for comfort care over high technology life prolonging treatment in an inpatient setting, 54% are still admitted to intensive care units.[10,11] More concerning was the fact that 57% of respondents stated that they would decline a subsequent life sustaining ICU admission in the event of a recurrent critical illness.[29] A 2006 study by Heyland et al. [12] identified that elderly Canadians value quality, not quantity of life, and do not want technology supported life prolonging measures. Canadian Intensive Care Units continue to mechanically ventilate and use life prolonging technology in the elderly, even when there is little chance of meaningful recovery. There is currently a significant disconnect between the wishes of the Canadian population and the ground level clinical practice. This discrepancy disrespects patient autonomy, and prolongs the dying process at significant expense to the health care system.

Our primary objective was to derive a clinical prediction tool to inform decision making at the time of ICU referral. Our prediction rule for hospital mortality in critically ill elderly patients is derived from the largest prospective dataset to date in this population. We used both academic and community ICUs and have evaluated its performance by internal validation.

The use of a robust clinical prediction tool can complement clinician judgment, enhance confidence in end-of-life decision making, optimize the alignment between goals of care and realistic clinical outcomes, and improve health care resource utilization.

Methods

Design and Setting

This is a secondary analysis of the REALISTIC-80 Study (Realities, Expectations and Attitudes to Life Support Technologies in Intensive Care for Octogenarians, clinicaltrials.gov NCT01293708) , a multicenter, prospective, observational cohort study conducted from September 2009 to February 2013. Twenty two Canadian academic and community ICUs participated. Waiver of informed consent was obtained from each local Research Ethics Board because the study is purely observational and poses no risk to participants. All patients over eighty years old who were admitted to ICU were eligible.

Study Population

We included a consecutive sample of all patients admitted to participating ICUs and who were 80 years of age or older. Enrollment began in September 2009, and was completed in February, 2012. Although data were gathered on medical , surgical emergency, and elective surgical patients, this paper will focus exclusively on the emergency surgical patients. Previously enrolled patients who were re-admitted to the ICU were not re-enrolled, as comprehensive data collection continued for 12 months following the index ICU admission. Routine local practices regarding criteria for ICU admission were maintained.

Baseline Data Collection

Trained research personnel collected data on the following outcomes for each study participant: age, sex, marital status, living status, APACHE II, [26] SOFA, [31] Functional Comorbidity Index, [32] Charlson Comorbidity Index, [33] admission type (medical, surgical emergency, surgical elective), following acute or chronic illness, length of hospital stay prior to ICU admission, primary ICU diagnosis, number of hospitalizations and emergency department visits in the preceding 12 months, serum albumin, body mass index, number of days in ICU, number of days in hospital, number of days of mechanical ventilation, vasoactive medication use, renal replacement therapy, and survival.

Survival was defined as being discharged from hospital, or alive in hospital one year post ICU admission. Early in the recruitment phase, funding allowed for each site to enroll a convenience sample of the first 60 eligible patients. Partway through the study, this number was decreased to 30 patients per site.

Data Analysis

Continuous variables were described by means, standard deviations, and ranges, with the exception of length of stay variables which were described by medians, quartiles, and ranges because of their positive skews. Categorical variables were described by counts and percentages. The association between predictors and the primary outcome was evaluated by univariable logistic regression. Continuous variables were categorized using the most discriminative cutpoints. Predictors with association P values < 0.2, that were deemed practical for routine emergency department of ward use and availability, and were felt to have high interobserver reliability were included in the multivariable logistic regression model. Interobserver reliability was not formally assessed in this derivation phase

Univariable analysis was used to evaluate the associations between predictor variables and the primary outcome (all cause hospital mortality). Continuous variables were categorized based on discriminative ability, and clinical sensibility. For example,

age was categorized into five year intervals between 80 and 90, and then > 90 because of the smaller n in that group. Statistical techniques for categorizing continuous variables are available[40], but the use of practical cutpoints with strong discriminative capacity may be preferable. Multivariable bidirectional stepwise logistic regression was performed using the predictors that were identified on univariable analysis as being associated with mortality ($p<0.2$), and felt to be widely available in most emergency departments or hospital wards (the usual ICU entry points for critically ill surgical patients).

The preliminary mortality risk stratification scale consists of simple elements that are easily available in emergency departments and hospital wards. Historical elements may be available from the patient, their chart, or their substitute decision maker. Clinical elements are obtained during patient examination. Metabolic elements are derived from simple blood tests. The risk scale used in this analysis was created by exponentiating the beta coefficients from the logistic regression model, then dividing all of the beta coefficients by the lowest beta coefficient value, and rounding the resultant values to the nearest whole number. In this manner, a relative risk scale was created[41,42].

SAS version 9.3 (SAS Institute, Cary, N.C., USA) was used for the statistical tests.

Results

There were 418 patients included in this study. No patients were lost while in the study hospitals. This high recruitment and follow up rates were due to the waived consent that was granted by each local Research Ethics Board (data could be extracted from the patient chart by research personnel, even after a patient death). All patients admitted to participating study sites during the enrollment period were included (Figure 3). Due to the ICU and hospital based nature of this study, there were no losses to follow up while patients were inpatients in the study centers. Participants who were transferred to non-study centers were lost to follow up. This is a significant limitation of this study and will be addressed in the discussion section.

The mean study patient age was 84.4, with a standard deviation of 3.4 and a range of 80.0-96.6. The participants were 53.6% male. They had significant illness acuity (mean Apache II 22.1). 45.2% had a gastrointestinal diagnosis, while 20.1% were admitted for cardiovascular / vascular reasons. Neurologic, trauma and orthopedic diagnoses comprised the bulk of the remaining participants (Table 12).

The median index ICU length of stay was 3.8 (IQR 6.3) days. Just under a fifth (18.7%) of patients did not survive to ICU discharge. Interestingly, patients worsened after their first ICU day (Mean Delta SOFA 1.0). Only a small proportion (6.9%) of all study participants were readmitted to the ICU if they survived their index admission (Table 13). The median index hospital length of stay was 20.1 (IQR 20.8) days. Hospital mortality (including those patients who died in the ICU) was 31.6%. Patients were considered survivors if they were still alive one year after their admission. Of the survivors, less than half (41.6%) were able to return home. A fifth (20.6%) of survivors required transfer to long-term care facilities. Another third of survivors (30.8%) were transferred to wards in other hospitals. Unfortunately, these patients were lost to further follow up and so were considered to have been discharged alive from hospital. Taking the worst case scenario approach (that all of these patients died soon after hospital transfer), would increase the hospital mortality from 31.6% to 62.4%. (Table 13)

Univariable Data Analysis

A univariable logistic regression analysis was performed using 13 of the Apache II components as the independent predictors and hospital mortality as the dependent variable. Age, gender, heart rate, and white blood cell count high were excluded on the basis of their P values of >0.05. (Table 14) White blood cell low was excluded from the multivariable analysis because of the low number of values. The respiratory rate values did not account for whether or not patients received mechanical (invasive or non-invasive) ventilation. For this reason, respiratory rate was excluded from further analysis because the sickest patients would have been mechanically ventilated, thereby

normalizing their respiratory rates. (the high respiratory rate did not have a statistically significant association with mortality, p=0.81)

Multivariable Data Analyses

The multivariable logistic regression model was developed using 212 (50.7%) of the 418 patients that were enrolled in the trial (Figure 3 and Table 15). The reason for this large loss of cases will be discussed in a subsequent section. Eight predictor variables from the univariable analysis were evaluated by bidirectional stepwise multivariable logistic regression. Three of the seven were statistically significant and will comprise the Preliminary Risk Scale. Kidney function was a very discriminative mortality predictor. Patients with serum creatinine levels of 120-300 had a mortality odds ratio of 2.83. Those with serum creatinine levels over 300 had a mortality odds ratio of 16.33 Serum pH was dichotomized to above and below 7.15. Patients with acidemia on arrival to the ICU had a mortality odds ratio of 6.0 with respect to their less acidemic counterparts

The Hosmer-Lemeshow chi-squared goodness-of-fit statistic was non-significant (p=0.9) which suggests a good fit to the data. The area under the receiver operating curve was 0.68 (95% CI 0.60-0.75) meaning that the model correctly classified 68% of cases for survival or mortality.

Preliminary risk scale

Our preliminary ICU mortality prediction tool consists of only two predictors: kidney function, and pH. The highest possible score is 5. (Table 16) A strength of the risk scale is its simplicity and the widespread and rapid availability of all its components. Some precision was lost by rounding the beta coefficients from the regression analysis, but we feel this is an acceptable concession for ease of use.

We found that the risk of hospital mortality ranged from 20.5% for a score of 0, to 100% for a total score of 2. (Table 17) We believe that due to the low sample size there were some deviations from a linear association between the observed mortality and our risk score.

The classification performance of our Preliminary Risk Scale is shown in Table 18. For each risk score, the number of study participants with each value, the scale's estimated probability of death, and the sensitivity and specificity of the prediction is shown. The sensitivity and specificity values for the probability of death are based on the risk score on Day 1 of ICU admission.

The classification performance of the final score categories was validated across 1000 replications with the bootstrap method.[43] (Table 19) The c statistic was 0.67 (95% CI 0.67-0.68), evidence of acceptable accuracy.

Discussion

Among the critically ill elderly patients in this cohort, we observed a significant hospital mortality that correlated with participants' Preliminary Risk Scale Scores for the low values. We identified that a small number of readily available predictors are strongly associated with hospital mortality: renal function, and serum pH. These high risk factors do not require sophisticated testing, advanced imaging or invasive procedures.

The classification performance of the Preliminary Risk Scale is very good at the low scores. Unfortunately, at scores of 2 and 3, the classification performance worsens. (Figure 4) The low number of patients with scores of 2 and 3 is the likely reason for this. In the clinical prediction tool that we derived for the medical patients in this study, there was a much greater n. This provided us with the ability to identify more clinically significant predictors that more accurately predicted hospital mortality.

We intend to perform an external validation phase with both our medical and surgical patients. We will likely divide the next cohort and use some of the data to improve our current prediction model in surgical patients.

How this Compliments the Literature

In some European countries, patients are already being refused ICU access on the basis of advanced age alone.[41] The Canadian Critical Care Research Network (CCCRNET) database of over 200 000 ICU admissions demonstrates an increase in the proportion of octogenarian admissions from 10% in 1994 to 14% in 2005.[34] An Ontario critical care database demonstrated that from 2006-2008, octogenarians comprised 18% of ICU admissions.[28] Ontario hospital ICU mortality data from 2001-2003 showed that one year after hospitalization, 48% of critically ill octogenarians had died, compared to a 23% ICU mortality in patients under 80 years of age.[20] In a single center, French study published in 2006, 180 critically ill octogenarians were followed to one year post hospital discharge. The hospital and 1 year mortality rates were 63% and 71%. Survivors described higher rates of depression, isolation, and lower mobility than an age and sex matched community cohort.

Clinical Implications

Our clinical prediction tool is intended to inform decision makers **at the time of ICU admission** regarding likely outcomes for critically ill elderly patients**.** In addition to providing an estimate of hospital mortality should maximal life support be instituted, the data from this trial will allow clinicians to educate decision makers regarding mean duration of ICU and hospital admission. Lastly, decision makers may be educated about the mean number of study patients who were able to return to independent living. The simplicity of the rule should improve its acceptance and implementation by clinicians, as emphasized in a previous similar study.[44] Any prediction rule that will be used to inform decisions regarding withholding or withdrawal of life sustaining therapy must demonstrate high specificity. This importance has been stressed in previous similar studies.[44]

Although the powerful predictive properties of a relatively small number of Apache II components has been demonstrated, the numerical values in this Risk Scale should not be used clinically until they have been externally validated. It does seem reasonable at this time for clinicians to use the mean survivorship data, and the components of the Risk Scale in clinical practice.

Study Strengths

Strengths of this study include the large number of participants, the large number of recruiting ICUs, and its prospective nature. Our clinical prediction rule has been derived from the largest prospective trial ever completed on critically ill octogenarians. It has shown very good predictive ability when internally validated via bootstrapping. This prediction rule does not require the presence of an accurate diagnosis, nor does it require any kind of neurologic evaluation beyond the well validated Glasgow Coma Score.[45] The risk scale is easy to remember, objective, and practical. As previously mentioned, when validated internally on 1000 bootstrap samples, the model performed reasonably well, particularly at the low end of expected hospital mortality.

Study Limitations

The Realistic 80 data used to derive the Preliminary Risk Tool were gathered on the first day of patients' ICU admission. Applying these data to a decision rule for use *prior to* ICU admission is imperfect. In most cases, the data are likely to be consistent with pre-admission values.

There was a great deal of missing data. This was due to the fact that participating centers were given the option of reporting either an aggregate Apache II score, or individual values. It turned out that nearly half of centers chose to report aggregate scores, and half reported the component data. It is our belief that this data should be considered missing completely at random. The ratio of predictors to events was not large enough to derive a meaningful Risk Tool. Tables describing the included and not included patients are available in the appendix.

Patients in the study who were transferred from the study hospital to another hospital were considered to have survived their hospital stay, because we were unable to follow their trajectories post transfer. This practice may have introduced some error as patients who died after transfer would be considered survivors and would bias our Risk Tool towards being overly optimistic.

Another study limitation stems from the fact that we only enrolled patients who were transferred to hospital and subsequently referred to and accepted by an ICU. This enrollment bias also contributed to an overly optimistic Risk Tool. All sick elderly patients who declined transfer to hospital (those that died at home, in nursing homes and hospices), whose physicians deemed them unsuitable for ICU (pre or post ICU referral), and those who were refused ICU admission on any grounds, would not have qualified as potential study participants.

Despite these limitations, we believe that the ability to provide decision makers with some objective, robustly derived data to educate them regarding mortality estimates, and ICU and hospital admission duration, is a significant advance for improving informed decision making.

Research Implications

We are pleased by the simplicity of our Preliminary Risk Scale, and its performance on the 1000 bootstrap samples. Figure 4 shows a reasonable relationship between our Risk Scale and the observed values in our sample. It is our hope and expectation that the model will be strengthened by the addition of more participants' data.

The next steps in our research are to strengthen the derivation with more data, and then to assess our Risk Scale's performance in an external sample taken from different institutions. No clinical prediction tool is ready for clinical implementation until it has undergone external validation. Future steps include an implementation phase to demonstrate the impact and penetration of the rule into routine clinical practice, an economic analysis to evaluate the financial implications of rule implementation, and a dissemination phase that includes strategies for knowledge translation to relevant audiences.

Conclusions

Critical care physicians are frequently asked by the families of critically ill elderly patients to help with end of life decision making. Implicit in these discussions are details regarding prognosis, survival chances, and eventual functional status. We have identified high risk characteristics for hospital mortality in the elderly population and developed a unique risk scale that can be used to inform goals of care and end of life meetings prior to implementation of the institution of life support. Once externally validated, this scale will benefit critically ill elderly patients, their families, and health care systems by improving end of life decision making and surgical planning.

Chapter 10 -- Discussion of the Prediction Tool for Surgical Emergency Patients

All of the medical patient prediction rule methodology and decision making discussion from chapter 7 of this thesis applies to the surgical emergency population as well. There are a few unique aspects to this group however. Elderly patients who are critically ill from a surgical emergency will generally die without surgical intervention. There are not any randomized trials to support this statement, nor will there ever be one for ethical reasons.

Another distinguishing feature between critically ill medical patients and surgical ones is the time pressure to make goals of care decisions. In the medical group, the intervention (ICU admission and management) is generally more prolonged. The urgency to begin treatment in the medical group is sometimes as acute as in their surgical counterparts, but often not.

The single biggest difference is the dichotomous nature of life saving surgery in critically ill elderly patients. They undergo the procedure or they don't. Once patients have undergone surgery (usually the most heroic and invasive aspect of their care), it seems reasonable that they be given some opportunity to convalesce. It may be considered inappropriate to submit a patient to the invasiveness of operative management (all critically ill patients receive life sustaining therapy intraoperatively), only to remove this therapy soon after.

Arguably, the combination of the decision making urgency and the dichotomous nature of surgery make a clinical prediction tool even more valuable in surgical patients than in medical ones. The heterogeneity of surgical emergencies makes one question the validity of a prediction rule. Could the heterogeneity of the Realistic 80 surgical patient population account for the small number of significant predictors, or was that merely a function of our low sample size?

Despite my concern for deriving a prediction tool for a group of patients with heterogeneous surgical emergencies, there are two features that are very reassuring. First, there is sound physiologic rationale for high mortality associated with critically ill elderly surgical patients that are acidemic and / or have renal dysfunction, irrespective of the cause of their surgical illness.

Secondly, if our rule performs well in a prospective validation, it will have stood the ultimate test. The previously mentioned concerns will be allayed.

Timing of Surgery

The other confounding aspect of the surgical prediction rule derivation is that the timing of the surgical intervention with respect to ICU admission was not taken into account.

Combining data from pre-operative critically ill elderly surgical emergency patients with those of post-operative critically ill elderly surgical emergency patients and subsequently applying it to all seems methodologically flawed. How to best approach this concern in the validation phase will be an important discussion topic during the study design. Options are to blend pre-operative and post-operative patient data together during the analysis versus evaluating them separately. A potential approach would be to evaluate the rule in the groups separately, and in combination.

In a validation study, patients who choose not to undergo emergency surgery / ICU admission should be followed for their outcomes, just as it was mentioned that following medical patients who choose to forego ICU admission should be followed.

Chapter 11 -- Methodologic Challenges in Realistic 80 Prediction Tool Derivation

As described throughout this thesis, the goal of designing prediction tools based on the Realistic 80 dataset is to inform end-of-life decision making *prior to* admission to the ICU and institution of life sustaining technology.
Although the derivation of clinical prediction tools was one of the many goals during the design phase of this prospective cohort study, it certainly was not the primary focus. Some steps that would normally be followed during the design of a prospective clinical prediction rule derivation were not included.

The gathering of a group of experts, both content experts and methodologic experts, with a focus on what data should be gathered, and when, is an important design step in prediction rule research. After speaking with the principal investigator of Realistic 80, this step was followed, but the group did not have a lot of prior experience with prediction rule studies.

Some key decisions were made in this trial design phase that have significantly impacted our ability to derive the prediction tool.

Enrollment in ICU Day 1

It is fairly standard for patients participating in ICU trials to be enrolled upon ICU admission. The problem that we are now facing is that we are trying to derive a prediction rule based on components of the patient demographics, history of presenting illness, and results of investigations, but our earliest investigations were performed *after ICU admission*. It is methodologically flawed to use data from *after ICU admission* to generate a rule that will be used clinically *prior to ICU admission.* There was some discussion about this challenge amongst the Canadian Critical Care Trials Group collaborators (my thesis supervisors were also involved) and the general consensus is that this practice really isn't methodologically sound. Even though the difference in time between when in the patients' clinical courses (immediately after ICU admission) blood work was drawn, and the time in their clinical courses in which the

derivation rule is intended to be applied (prior to ICU admission), is very small, much can change with the onset of aggressive resuscitation, endotracheal intubation and mechanical ventilation, institution of vasoactive agents, etc.

ICU Specific Covariates

In addition, many of the covariates that were recorded in the study are very ICU specific, being frequently unavailable on the wards or emergency departments (arterial PO_2, P/F ratio), or simply not commonly used outside the ICU (Charleson comorbidity index, functional index, SOFA score). By not including these potential predictors in the prediction rule derivation, much of the available data was not used. This was not optimal, but this decision was made because any rule with components that are not routinely available in the setting for which it is intended to be used will have limited utility.

Missing Data – Aggregate versus Component Reporting of APACHE II

This third challenge of nearly half the study participants having missing data because of the discrepancy in how the APACHE II scores were reported has been previously discussed. Fortunately there is a sound argument for this data being classified as MCAR, but nonetheless our sample size was significantly reduced from what we had originally anticipated. The impact of missing data had the most repercussions on the surgical prediction tool derivation.

Patients Transferred Out of Study Hospitals

Nearly a quarter of all patients were transferred from a study hospital to a non-study hospital and subsequently lost to follow-up. This is a significant threat to our data. For the purposes of our prediction rule derivations, these patients were considered alive, but the reality could be quite different. This large loss to follow up could have been prevented (or at least attenuated) in the early phases of trial design. It has biased our prediction rules to being overly optimistic regarding mortality outcomes.

Chapter 12 -- Summary and Conclusions

Technological advances in the past 50 years have progressed at a remarkable rate. So too have the therapies available within medicine and surgery. As technology evolves, people's expectations for rapid solutions have followed. It strikes me that the expression "she died of old age" has become very uncommonly used by laypeople, just as the words "there is nothing more that we can do" have become less commonly spoken by physicians and surgeons.

It is wonderful that more patients are being cured of cancer, surviving their heart attacks and strokes with a higher quality of life than previously, or being discharged home from ICUs after bouts of severe sepsis.

It is very evident in the ICU environment that what is starting to be forgotten is that despite our technological advances, life remains finite. We can't now, nor will we ever be able to, cure all illnesses. It is more important now than ever before that clinicians be sensitive and open about this fact during end of life discussions with patients and their families.

The challenge for clinicians is knowing when and when not to, institute high technology treatments when caring for critically ill elderly patients. For those patients who want life support, and who have a reasonable chance of improving, they should be treated with aggressive medical therapy, including life sustaining measures in an ICU environment. But for those patients not wanting high technology treatment, and for those at the end of their lives, ICU admission is simply inappropriate.

A two pronged approach to this challenge is required. The first, and likely more important facet, is the enhancement of end-of-life discussions between clinicians and patient families. These need to be open, compassionate dialogues that are targeted at the appropriate level of family understanding. Helping to inform these discussions is the role of our clinical prediction tools.

Like technology, clinical prediction rule science had evolved tremendously over

the past three decades. Ottawa knee [59] and ankle rules [60], Canadian CT head [61] and C-spine rules [58], pneumonia prediction tools [57], DVT [62] and PE scores [63], as well as Acetaminophen poisoning nomograms [64] are used daily in emergency medicine and trauma.

The challenge with ICU / hospital survival is that it is a dynamic target. A patient's outcome is affected by unknown patient factors, physician factors, and institution factors. In addition, critical care is a multidisciplinary environment where standards of care and technologies are constantly improving. It is impossible to produce a prediction tool that could be perfectly accurate in such a dynamic, heterogeneous patient population.

A common criticism of a prediction rule for survival is that it isn't very useful for the middle eighty percent of the patients, which constitutes the majority. Knowing that a patient's predicted mortality is over 90% or less than 10% is a lot more likely to influence decision making than a predicted mortality of 70% for example. I accept this criticism and agree that the rule is a lot more useful at the extremes. I still maintain that having an estimated mortality, knowledge of the mean ICU and hospital length of stays, and an estimated chance for return to independent living is a tremendous improvement for informing end of life discussions than status quo.

The goal of our prediction tool is to complement clinician's clinical judgment, and strengthen the conviction with which they speak to families. In addition to prediction rule derivation, the Realistic 80 data can help end of life decision making by describing outcomes such as mean length of ICU and hospital stay, as well as mean rates of return to independent living. Though far from perfect, these objective, evidence based data are a definite improvement over physician experience in isolation.

Chapter 13 -- Future Steps

The three manuscripts described in this thesis provide descriptions of the patient outcomes, and the derivation of risk scales for predicting mortality in both critically ill medical, and surgical patients. A 2009 systematic review of published prediction rules [37] demonstrated that none of them had been prospectively validated in a separate population. This is a fundamental tenet of prediction rule science if the goal is clinical implementation.

As such, I will be applying to granting agencies to support a prospective, multi center validation trial of our prediction rules.

In addition to a validation trial, an economic analysis of the potential impact of our rule's implementation (if it helps clinicians and family members avoid futile ICU admissions) will be undertaken.

Working with the knowledge translation section of the Canadian Critical Care Trials group in an effort to disseminate our rule will complement its exposure to clinicians through journal publications and conference presentations.

Tables

Table 1 – Patient Demographics Categorized by Admission Diagnosis

	Medical (n=1033)	Surgical elective (n=220)	Surgical emergency (n=418)	All patients n=1671
Age in years*	84.6±3.5 (79.9-100.2)	84.0±3.2 (80.0-95.9)	84.4±3.4 (80.0-96.6)	84.5±3.2 (79.9,100.2)
Sex				
Male	568 (55.0%)	123 (55.9%)	224 (53.6%)	915 (54.8%)
Female	465 (45.0%)	97 (44.1%)	194 (46.4%)	756 (45.2%)
Baseline APACHE II*	23.1±7.9	19.5±7.1	22.1±7.2	22.4±7.7
Charleson Co-morbidity Index*	2.2±1.8	1.9±1.9	1.9±1.9	2.1±1.8
Functional Co-morbidity Index*	1.9±1.4	1.8±1.3	1.7±1.4	1.8±1.4
Pre-ICU Albumin *(g/l)**	29.5±7.2	32.3±8.4	28.7±6.8	29.6±7.3
Pre-ICU Hemoglobin *(g/L)**	114.1±25.9	112.4±26.1	114.3±27.0	114.0±26.2
Baseline SOFA score*	5.3±3.4	4.8±2.9	5.4±3.3	5.3±3.3
Primary ICU diagnosis				
Cardiovascular/vascular	212 (20.5%)	112 (50.9%)	84 (20.1%)	408 (24.4%)
Respiratory	361 (34.9%)	16 (7.3%)	12 (2.9%)	389 (23.3%)
Gastrointestinal	74 (7.2%)	35 (15.9%)	189 (45.2%)	298 (17.8%)
Neurologic	114 (11.0%)	17 (7.7%)	55 (13.2%)	186 (11.1%)
Sepsis	171 (16.6%)	5 (2.3%)	2 (0.5%)	178 (10.7%)
Trauma	37 (3.6%)	0 (0.0%)	37 (8.9%)	74 (4.4%)
Orthopedic	2 (0.2%)	29 (13.2%)	36 (8.6%)	67 (4.0%)
Hematologic	43 (4.2%)	0 (0.0%)	0 (0.0%)	43 (2.6%)
Metabolic	18 (1.7%)	0 (0.0%)	0 (0.0%)	18 (1.1%)
Renal	1 (0.1%)	5 (2.3%)	3 (0.7%)	9 (0.5%)
Gynecologic	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.1%)

**mean ± sd (min, max)*

Table 2: Processes of ICU Care

	Medical (n=1033)	Surgical Elective (n=220)	Surgical Emergency (n=418)	All Patients (n=1671)
Mean Days from ICU Admission to First Withhold or Withdrawal Order in ICU	5.1+/-7.7	6.8+/-8.6	4.8+/-5.5	5.2+/-7.3
Mean Days from First Withhold or Withdrawal Order in ICU to Death	6.5+/-9.7	4.6+/-4.9	6.8+/-10.1	6.5+/-9.7
Received Vasopressors				
Yes (%)	587 (56.8%)	128 (58.2%)	227 (54.3%)	942 (56.4%)
Duration (days)*	3.7+/-3.7	3.5+/-4.6	3.6+/-3.1	3.7+/-3.7
Non-Invasive Ventilation				
Yes (%)	199 (19.3%)	18 (8.2%)	41 (9.8%)	258 (15.4%)
Duration (days)*	3.3+/-3.9	3.1+/-2.9	3.0+/-2.9	3.2+/-3.7
Invasive Ventilation				
Yes (%)	693 (67.1%)	152 (69.1%)	356 (85.2%)	1201 (71.9%)
Duration (days)*	8.2 (17.3)	4.8+/-7.9	6.0+/-7.6	7.1+/-14.1
Received Dialysis				
Yes (%)	78 (7.6%)	8 (3.6%)	17 (4.1%)	103 (6.2%)
Duration (days)*	12.0+/-18.2	17.0+/-16.1	13.9+/-22.6	12.7+/-18.6
Withheld at ICU Admission				
Vasopressor	28 (2.7%)	2 (0.9%)	4 (1.0%)	34 (2.0%)
Ventilator	73 (7.1%)	4 (1.8%)	9 (2.2%)	86 (5.1%)
Dialysis	29 (2.8%)	1 (0.5%)	8 (1.9%)	38 (2.3%)
CPR	216 (20.9%)	12 (5.5%)	69 (16.5%)	297 (17.8%)
No life-sustaining therapies withheld	814 (78.8%)	208 (94.5%)	349 (83.5%)	1371 (82.0%)
Withheld After ICU Admission to ICU Discharge or ICU Death				
Vasopressor	132 (12.8%)	9 (4.1%)	29 (6.9%)	170 (10.2%)
Ventilation	147 (14.2%)	13 (5.9%)	37 (8.9%)	197 (11.8%)
Dialysis	110	8 (3.6%)	35 (8.4%)	153 (9.2%)

	(10.6%)			
CPR	311 (30.1%)	20 (.1%)	96 (23.0%)	427 (25.6%)
No life-sustaining therapies withheld	672 (65.1%)	195 (88.6%)	309 (73.9%)	1176 (70.4%)
Withdrawn After ICU Admission to ICU Discharge or ICU Death				
Vasopressor	112 (10.8%)	6 (2.7%)	40 (9.6%)	158 (9.5%)
Ventilation	184 (17.8%)	7 (3.2%)	45 (10.8%)	236 (14.1%)
Dialysis	19 (1.8%)	1 (0.5%)	11 (2.6%)	31 (1.9%)
CPR	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
No life-sustaining therapies withheld	823 (79.7%)	210 (95.5%)	362 (86.6%)	1395 (83.5%)
*mean +/-sd				

Table 3: Clinical Outcomes

	Medical (n=1033)	Surgical elective (n=220)	Surgical emergency (n=418)	All patients n=1671
Baseline SOFA*	5.3±3.4	4.8±2.9	5.4±3.3	5.3±3.3
Maximum SOFA*	6.2±3.7	5.6±3.2	6.3±3.6	6.1±3.6
Delta SOFA*	0.8±1.6	0.8±1.6	1.0±1.8	0.9±1.6
Index ICU Length of Stay (days)**	4.0 (5.9)	2.1 (3.7)	3.8 (6.3)	3.7 (5.8)
Total ICU Length of Stay (days) **	4.1 (6.2)	2.4 (3.9)	3.8 (6.7)	3.8 (6.0)
Patients with at least one ICU readmission (%)	59 (5.7%)	14 (6.4%)	29 (6.9%)	102 (6.1%)
Hospital Length of Stay (days) **	16.2 (25.0)	13.0 (15.0)	20.1 (28.8)	16.6 (24.8)
ICU mortality (%)	274 (26.5%)	13 (5.9%)	78 (18.7%)	365 (21.8%)
Hospital mortality (%)	429 (41.5%)	24 (10.9%)	132 (31.6%)	585 (35.0%)
Discharged from Hospital to (%of total discharged)				
Ward in another hospital	149 (24.7%)	51 (26.0%)	88 (30.8%)	288 (26.5%)
ICU in another hospital	20 (3.3%)	1 (0.5%)	9 (3.1%)	30 (2.8%)
Long term care facility	136 (22.5%)	21 (10.7%)	59 (20.6%)	216 (19.9%)
Home	272 (45.0%)	113 (57.7%)	119 (41.6%)	504 (46.4%)
Rehab	22 (3.6%)	3 (1.5%)	9 (3.1%)	34 (3.1%)
Palliative Care	4 (0.7%)	2 (1.0%)	1 (0.3%)	7 (0.6%)
Other	1 (0.2%)	5 (2.6%)	1 (0.3%)	7 (0.6%)

**mean ± sd*
***median (IQR)*

Table 4: Characteristics of 1033 Medical Patients Admitted to the ICU

	Number of patients (n=1033)
Age in years*	84.6 +/- 3.5
Age range	79.9 – 100.2
Male (%)	568 (55.0)
Baseline APACHE II*	23.1 +/- 7.9
Charleson Co-morbidity Index*	2.2 +/-1.8
Functional Co-morbidity Index*	1.9 +/- 1.4
Pre-ICU Albumin *(g/L)**	29.5 +/-7.2
Pre-ICU Hemoglobin *(g/L)**	114.1+/-25.9
Baseline SOFA score*	5.3+/-3.4
Primary ICU diagnosis (%)	212 (20.5)
Cardiovascular/vascular	361 (34.9)
Respiratory	74 (7.2)
Gastrointestinal	114 (11.0)
Neurologic	171 (16.6)
Sepsis	37 (3.6)
Trauma	2 (0.2)
Orthopedic	43 (4.2)
Hematologic	18 (1.7)
Metabolic	1 (0.1)
Renal	0 (0)
Gynecologic	0 (0)
*value +/- std deviation	

Figure 1: Flow Diagram

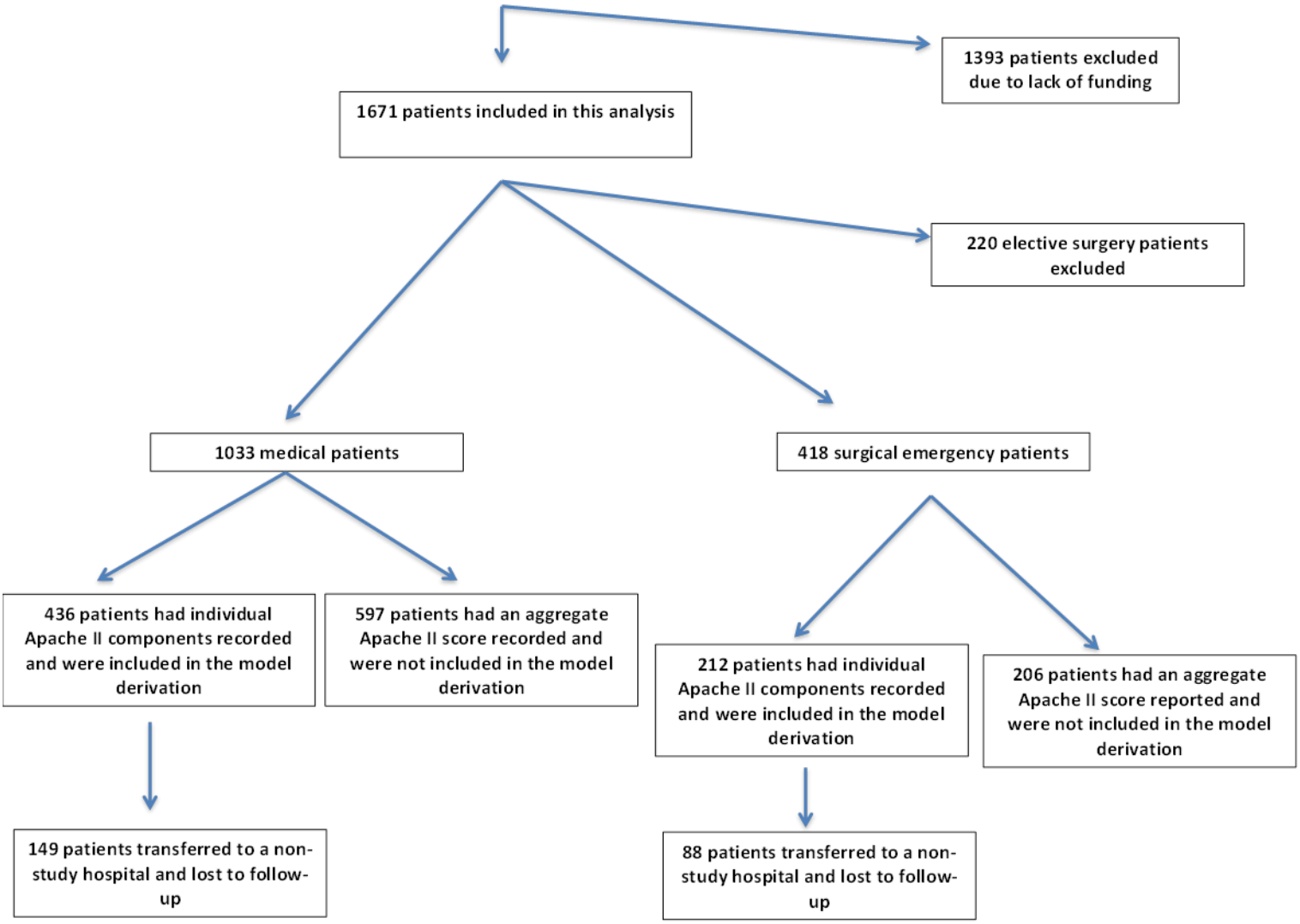


Table 5: Outcomes of the 1033 Medical Patients

SOFA (Mean Value +/- SD (range))	
Baseline SOFA	5.3+/-3.4 (0.0-15.0)
Maximum SOFA	6.2+/-3.7 (0.0-18.0)
Delta SOFA	0.8+/-1.6 (0.0-13.0)
Length of Stay (Median (IQR))	
Index ICU LOS	4.0 (5.9)
Total ICU LOS	4.1 (6.2)
Hospital LOS	16.2 (25.0)
Patients with at least 1 ICU Readmission (% of total number of patients)	59 (5.7)
Mortality (%)	
ICU Mortality	274 (26.5)
Hospital Mortality	429 (41.5)
Survivor Discharge Disposition (%)	
Ward in another hospital	149 (24.7)
ICU in another hospital	20 (3.3)
Long term care facility	136 (22.5)
Home	272 (45)
Rehab	22 (3.6)
Palliative Care	4 (0.7)
Other	1 (0.2)

Table 6: Univariable Analysis for Variables Associated with All Cause Hospital Mortality

Variable	Number of Patients	Value	Deaths (%)	OR (95% CI)	P-Value
Age	1028				0.05
Gender	465	Female	194 (41.7%)	1.01 (0.79-1.30)	0.91
GCS	594				<0.0001
Heart Rate	593				0.001
	253	50-99	86 (34.0%)	Referent	
	281	100-140	131 (46.6%)	1.70 (1.20, 2.41)	
	59	>140	33 (55.9%)	2.47 (1.39, 4.38)	
Respiratory Rate	593				0.002
	114	10-20	37 (32.5%)	Referent	
	302	21-30	119 (39.4%)	1.35 (0.86, 2.13)	
	149	31-40	75 (50.3%)	2.11 (1.27, 3.50)	
	28	>40	18 (64.3%)	3.75 (1.57, 8.91)	
Received Vasoactive Medication	503	Yes	251 (49.9%)	1.97 (1.53, 2.53)	<0.0001
Serum pH	442				<0.0001
	398	>/=7.15	174 (43.7%)	Referent	
	44	<7.15	34 (77.3%)	4.38 (2.10, 2.41)	
Serum Creatinine	594				<0.0001
	290	<120	101 (34.8%)	Referent	
	251	120-300	113 (45.0%)	1.53 (1.08, 2.17)	
Serum Sodium High	577				0.12
	490	131-145	201 (41.0%)	Referent	
	65	146-150	27 (41.5%)	1.02 (0.60, 1.73)	
	22	>150	14 (63.6%)	2.52 (1.04, 6.11)	
Serum Potassium	570				0.12

Low					
	539	3.0-5.0	219 (40.6%)	Referent	
	31	<3.0	18 (58.1%)	2.02 (0.97, 4.21)	
Serum Potassium High	590				0.07
	503	2.9-5.0	200 (39.8%)	Referent	
	75	5.0-6.5	40 (53.3%)	1.73 (1.06, 2.82)	
	12	>/=6.5	6 (50.0%)	1.52 (0.48, 4.76)	
WBC Low	278				0.0009
	252	4.0-10.0	93 (36.9%)	Referent	
	26	<4.0	19 (73.1%)	4.64 (1.88, 11.45)	
WBC High	583				0.13
	158	4.0-10.0	56 (35.4%)	Referent	
	297	10.1-20.0	126 (42.4%)	1.34 (0.90, 2.00)	
	83	20.1-30.0	39 (47.0%)	1.61 (0.94, 2.77)	
	25	30.1-40.0	8 (32.0%)	0.86 (0.35, 2.11)	
	20	>40.0	12 (60.0%)	2.73 (1.05, 7.08)	

Table 7: Independent Predictors of All Cause Hospital Mortality, As Determined by Stepwise Logistic Regression

Variable	Beta Coefficient	Odds Ratio (95% CI)
Age in Years		
80-84	referent	
85-90	0.49	1.63 (1.04-2.56)
>90	0.97	2.64 (1.27-5.48)
Serum Creatinine		
<120	referent	
120-300	0.45	1.57 (1.01-2.44)
>300	1.67	5.29 (2.43-11.51)
GCS		
15	referent	
13-14	0.73	2.09 (1.09-3.98)
8-12	0.84	2.31 (1.34-3.97)
4-7	1.75	5.75 (3.02-10.95)
3	2.19	8.97 (3.70-21.74)
Serum pH		
>/= 7.15	referent	
<7.15	0.89	2.44 (1.07-5.60)

Table 8: Risk Scale for Mortality in Critically Ill Elderly Patients

Age	**Points**
85-89	1
>90	2
Level of Alertness (GCS)	
8-14	2
4-8	4
3	5
Metabolic Function	
Creatinine 120-300	1
Creatinine > 300	4
pH<7.15	2

Table 9: Risk Categories for Hospital Mortality in Critically Ill Medical Patients

Total Score	Risk of Hospital Mortality (%)	Risk Category
0	25.6	Low
1	21.8	Low
2	31.8	Moderate
3	48.0	Moderate
4	50.9	Moderate
5	53.5	Moderate
6	74.3	High
7	100.0	Very High
8	91.7	Very High
9	75.0	Very High
10	100.0	Very High
11	*	*
12	100.0	Very High

*no patients had a total score of 11.

Table 10: Classification Performance for Preliminary Risk Scale

Total Score	No. of patients	Sensitivity (%)	Specificity (%)	Estimated Probability of Death (%)
0	39	100	0	18.5
1	55	94.7	13.6	25.4
2	63	88.4	33.6	33.9
3	75	77.8	53.7	43.5
4	59	58.7	72.0	53.7
5	43	42.9	85.5	63.6
6	35	30.7	94.9	72.4
7	9	16.9	99.1	79.8
8	12	12.2	99.1	85.6
9	4	6.3	99.5	89.9
10	8	4.8	100.0	93.1
11	0	N/A	N/A	N/A
12	1	0.5	100.0	96.8

Table 11: Internal Validation of the Risk Scale by Bootstrapping

	Bootstrap AUC	Full Model AUC	AUC Optimism	Bootstrap Adjusted R^2	Full Model Adjusted R^2	Adjusted R^2 Optimism
N	1000	1000	1000	1000	1000	1000
Minimum	0.63	0.72	-0.10	0.08	0.20	-0.09
Maximum	0.80	0.72	0.08	0.36	0.21	0.18
Mean	0.72	0.72	0.00	0.21	0.20	0.01
Std Deviation	0.03	0	0.03	0.04	0.01	0.04

Figure 2: Observed Versus Expected Probability of Hospital Mortality in Critically Ill Elderly Medical Patients

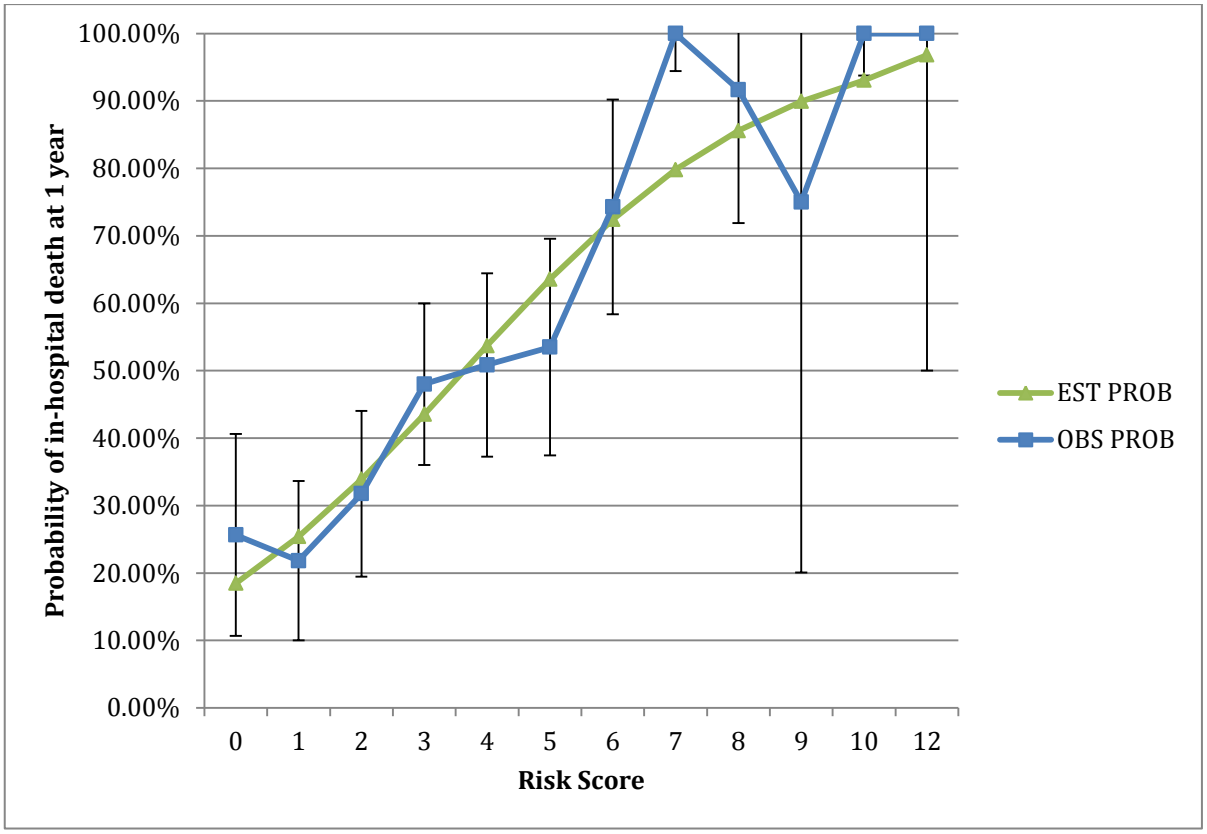


Table 12: Characteristics of the Surgical Emergency Patients

	Number of patients (n=418)
Age in years*	84.4±3.4
Age range	80.0 – 96.6
Male (%)	224 (53.6%)
Baseline APACHE II*	22.1+/-7.2
Charleson Co-morbidity Index*	1.9+/-1.9
Functional Co-morbidity Index *	1.7+/-1.4
Pre-ICU Albumin *(g/L)**	28.7+/-6.8
Pre-ICU Hemoglobin *(g/L)**	114.3+/-27.0
Baseline SOFA score *	5.4+/-3.3
Primary ICU diagnosis (%)	
Cardiovascular/vascular	84 (20.1%)
Respiratory	12 (7.2%)
Gastrointestinal	189 (45.2%)
Neurologic	55 (13.2%)
Sepsis	2 (0.5%)
Trauma	37 (8.9%)
Orthopedic	36 (8.6%)
Hematologic	0 (0.0%)
Metabolic	0 (0.0%)
Renal	3 (0.7%)
Gynecologic	0 (0.0%)
*value +/- std deviation	

Figure 3: Flow Diagram

3064 eligible patients admitted to participating ICUs during study period

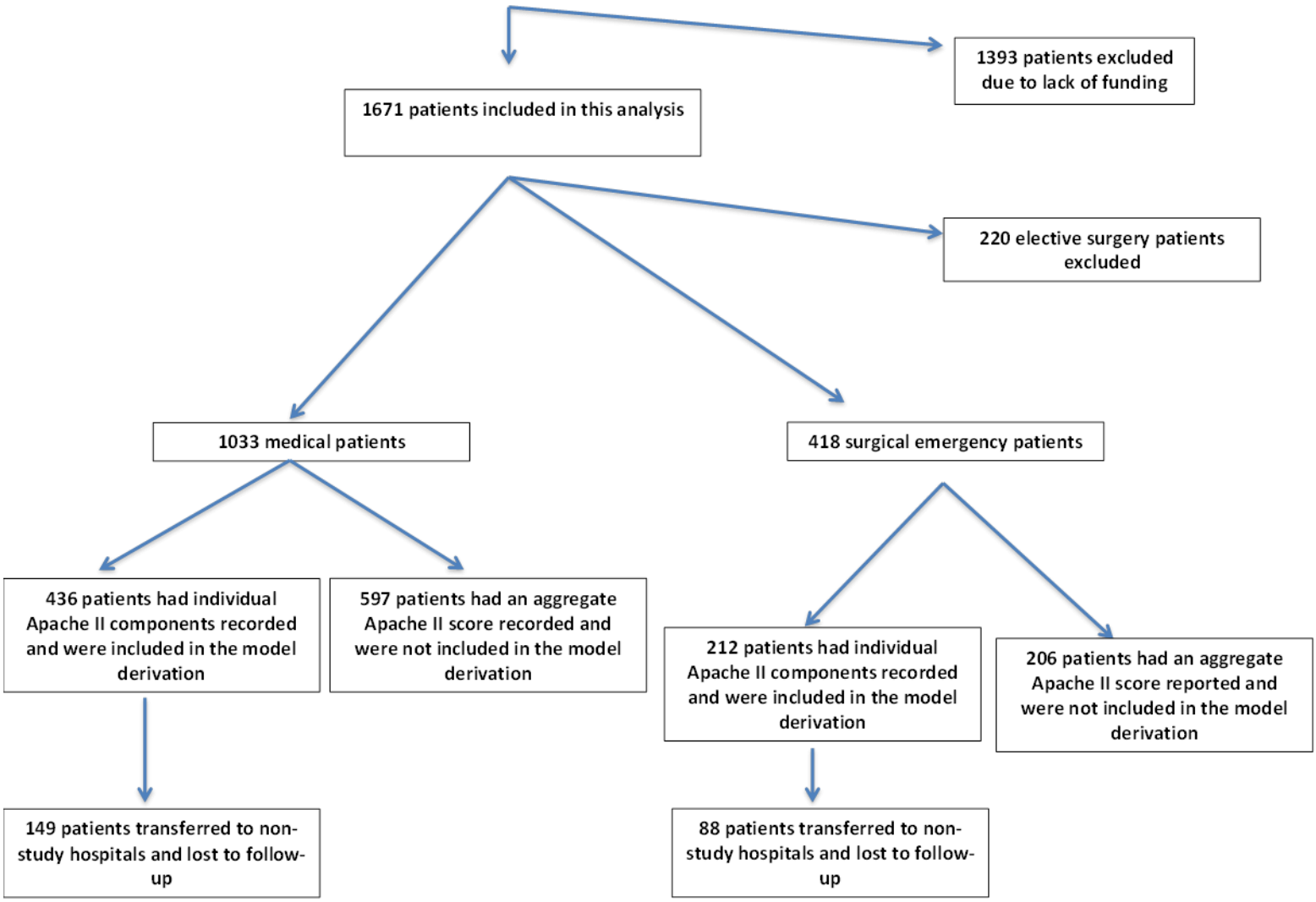


Table 13: Outcomes of the 418 Surgical Emergency Patients

SOFA (Mean Value +/- SD (range))	
Baseline SOFA	5.4+/-3.3 (0.0-17.0)
Maximum SOFA	6.3+/-3.6 (0.0-17.0)
Delta SOFA	1.0+/-1.8 (0.0-12.0)
Length of Stay (Median Days (IQR))	
Index ICU LOS	3.8 (6.3)
Total ICU LOS	3.8 (6.7)
Hospital LOS	20.1 (28.8)
Patients with at least 1 ICU Readmission (% of total number of patients)	29 (6.9)
Mortality (%)	
ICU Mortality	78 (18.7)
Hospital Mortality	132 (31.6)
Discharge Disposition (%)	
Ward in another hospital	88 (30.8)
ICU in another hospital	9 (3.1)
Long term care facility	59 (20.6)
Home	119 (41.6)
Rehab	9 (3.1)
Palliative Care	1 (0.3)
Other	1 (0.3)

Table 14: Univariable Analysis for Variables Associated with All Cause Hospital Mortality

Variable	Number of Patients	Value	Deaths (%)	OR (95% CI)	P Value
Age	418				0.31
	226	80-84	66 (29.2%)	Referent	
	146	85-89	53 (36.3%)	1.38 (0.89, 2.15)	
	46	>89	13 (28.3%)	0.96 (0.47, 1.93)	
Gender	194	Female	56 (28.9%)	0.79 (0.52, 1.20)	0.27
GCS	224				0.003
	88	15	19 (21.6%)	Referent	
	31	13-14	10 (32.1%)	1.73 (0.70, 4.29)	
	55	8-12	16 (29.1%)	1.49 (0.69, 3.23)	
	17	4-7	13 (76.5%)	11.80 (3.45, 40.39)	
	33	3	11 (33.3%)	1.82 (0.75, 4.40)	
Heart Rate Low	215				0.09
	194	50-99	57 (29.4%)	Referent	
	21	<50	10 (47.6%)	2.19 (0.88, 5.43)	
Heart Rate High	224				0.58
	93	50-99	29 (31.2%)	Referent	
	117	100-139	34 (29.1%)	0.90 (0.50, 1.64)	
	14	>139	6 (42.9%)	1.66 (0.53, 5.21)	
Respiratory Rate High	223				0.81
	84	10-20	27 (32.1%)	Referent	
	118	21-30	34 (28.8%)	0.85 (0.47, 1.57)	
	17	31-40	5	0.88 (0.28,	

			(29.4%)	2.75)	
	4	>40	2 (50.0%)	2.11 (0.28, 15.80)	
Received Vasoactive Medication	418				<0.0001
	190	Yes	80 (42.1%)	2.46 (1.61, 3.76)	
Serum pH	212				0.009
	201	>7.15	61 (30.4%)	Referent	
Serum Creatinine	223				0.0009
	142	<120	32 (22.5%)	Referent	
	74	120-300	32 (43.2%)	2.62 (1.43, 4.80)	
	7	>300	5 (71.4%)	8.59 (1.59, 46.41)	
WBC High	218				0.07
	53	4.0-10.0	14 (26.4%)	Referent	
	123	10.1-20.0	33 (26.8%)	1.02 (0.49, 2.12)	
	35	20.1-30.0	16 (45.7%)	2.35 (0.95, 5.79)	
	7	>30.0	4 (57.1%)	3.71 (0.74, 18.71)	

Table 15: Independent Predictors of All Cause Hospital Mortality, As Determined by Stepwise Logistic Regression

Variable	Beta Coefficient	Odds Ratio (95% CI)
Creatinine 120-300	1.04	2.83 (1.41-5.68)
Creatinine >300	2.79	16.33 (2.5-106.24)
pH < 7.15	1.79	6.00 (1.34-26.85)

Table 16: Risk Scale for Mortality in Critically Ill Elderly Surgical Patients

Serum Creatinine	**Points**
120-300	1
> 300	3
Serum pH	
<7.15	2

Table 17: Risk Categories for Hospital Mortality in Critically Ill Surgical Patients

Total Score	Hospital Mortality (%)	Risk Category
0	20.5	low
1	46.3	moderate
2	100	extremely high
3	62.5	moderate

Table 18: Classification Performance for Preliminary Risk Scale

Total Score	No. of patients	Sensitivity (%)	Specificity (%)	Estimated Probability of Death (%)
0	122	100	0	22.2
1	67	61.5	71.3	42.7
2	4	13.8	97.8	66.2
3	8	7.7	97.8	83.7

Table 19: Internal Validation of the Risk Scale by Bootstrapping

	Bootstrap AUC	Full Model AUC	AUC Optimism	Bootstrap Adjusted R^2	Full Model Adjusted R^2	Adjusted R^2 Optimism
N	1000	1000	1000	1000	1000	1000
Minimum	0.54	0.68	-0.14	0.00	0.01	-0.07
Maximum	0.78	0.68	0.10	0.34	0.13	0.31
Mean	0.68	0.68	0.00	0.14	0.12	0.02
Standard Deviation	0.04	0	0.04	0.06	0.02	0.07

Figure 4: Observed Versus Expected Probability of Hospital Mortality in Critically Ill Elderly Surgical Patients

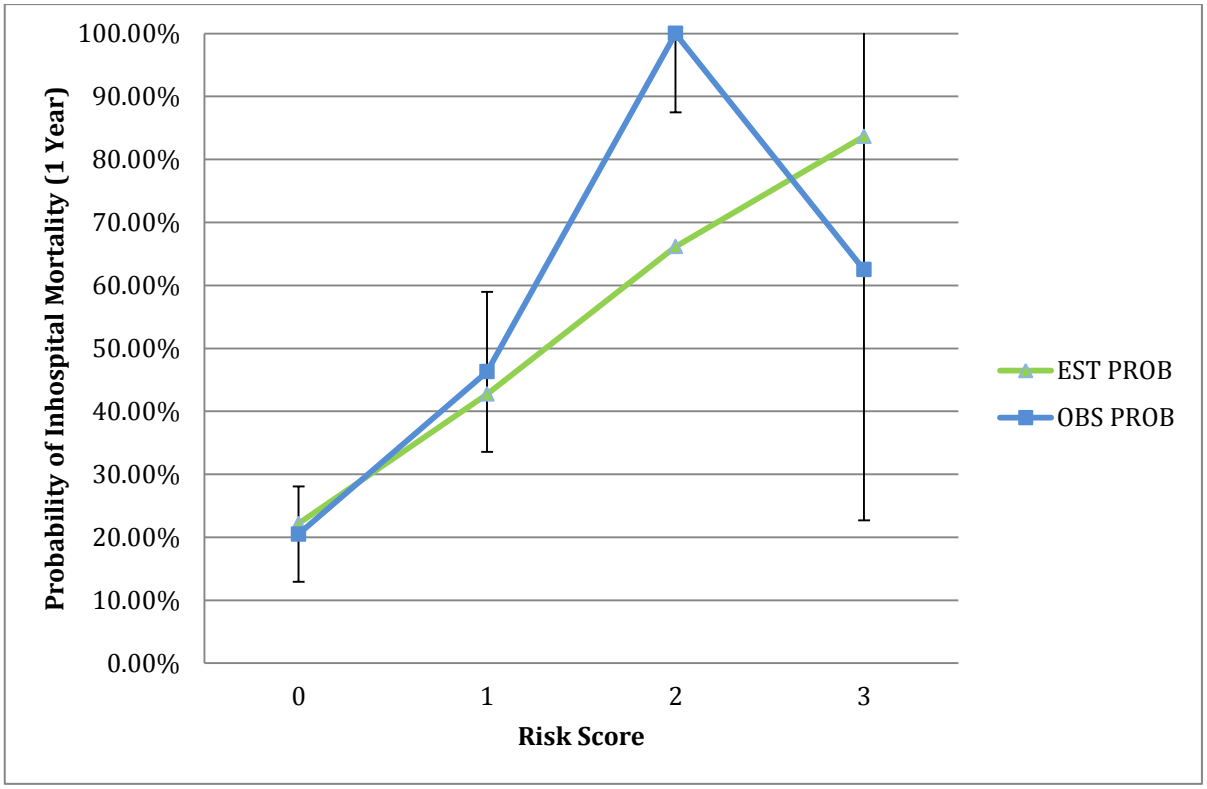
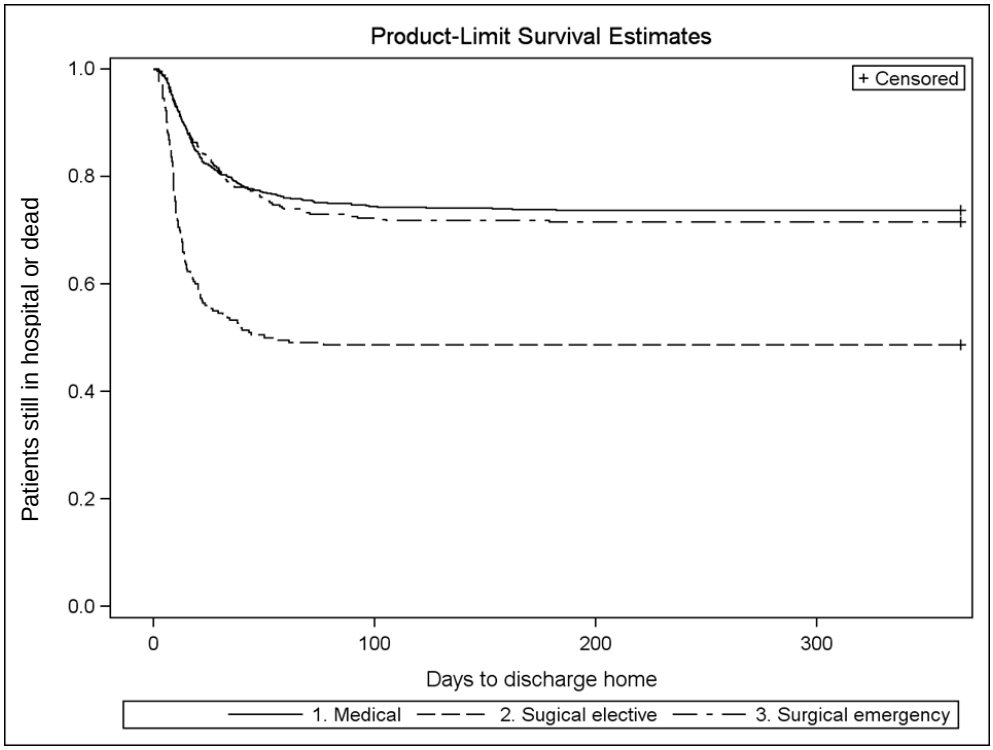


Figure 5 – Kaplan Meyer Curves by Etiology of Critical Illness



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Appendix

Appendix Figure 1 – Univariate Analysis of Survivors vs. Non-Survivors for Medical and Surgical Patients Combined

		Survivors (n=1086)	Non-Survivors (n=585)	P Value
Age				
	Mean +/-SD (n)	84.3+/-3.3 (1086)	84.9 +/-3.6 (585)	<0.001
Sex				0.63
	male	590 (54.3%)	325 (55.6%)	
	female	496 (45.7%)	260 (44.4%)	
Admission Type				<0.001
	Medical	604 (55.6%)	429 (73.3%)	<0.001
	Surgical elective	196 (18.0%)	24 (4.1%)	<0.001
	Surgical emergency	286 (26.3%)	132 (22.6%)	0.09
Eye (GCS)				
	Mean +/-SD (n)	3.5 +/-1.0 (638)	2.9+/-1.3 (330)	<0.001
Verbal (GCS)				
	Mean +/-SD (n)	3.7 +/-1.7 (638)	2.7+/-1.8(330)	<0.001
Motor (GCS)				
	Mean +/-SD (n)	5.4 +/-1.5 (638)	4.6+/-1.8(330)	<0.001
Heart Rate Low				
	Mean +/-SD (n)	69.3 +/-14.6 (636)	71.8+/-18.8 (332)	0.12
Heart Rate High				
	Mean +/-SD (n)	103+/-29.1 (636)	109.2+/-26.6 (332)	<0.001
Respiratory Rate Low				
	Mean +/-SD (n)	12.9+/-4.3 (635)	14.7+/-4.9 (331)	<0.001

Respiratory Rate High				
	Mean +/-SD (n)	25.0+/-6.8 (635)	28.7+/-17.1 (331)	<0.001
On Any Vasopressor at Time of ICU Admission				<0.001
	No	621 (57.2%)	240 (41.0%)	
	Yes	465 (42.8%)	345 (59.0%)	
HCO_3 Low (venous – mmol/L)				0.35
	Mean +/-SD (n)	24.3+/-5.5 (87)	23.2+/-4.6 (37)	
HCO_3 High (venous – mmol/L)				
	Mean +/-SD (n)	26.0+/-6.5 (87)	24.7+/-4.2 (37)	0.51
PaO_2 Low				
	Mean +/-SD (n)	97.8+/-48.1 (504)	93.4+/-53.1 (287)	0.02
PaO_2 High				
	Mean +/-SD (n)	144.4+/-71.5 (504)	139.8+/-75.7 (287)	0.22
Arterial pH Low				
	Mean +/-SD (n)	7.3+/-0.1 (507)	7.3+/-0.1 (289)	<0.001
Arterial pH High				
	Mean +/-SD (n)	7.4+/-0.1 (507)	7.4+/-0.1 (289)	0.08
Serum Creatinine Low				
	Mean +/-SD (n)	113.2+/-87.5 (635)	148.4+/-109.2 (332)	<0.001
Serum Creatinine High				
	Mean +/-SD (n)	130.9+/-110.6 (635)	173.0+/-130.8 (332)	<0.001
Serum Sodium Low				
	Mean +/-SD (n)	137.0+/-9.7 (633)	137.2+/-11.1 (332)	0.35
Serum Sodium High				
	Mean +/-SD (n)	139.4+/-9.8 (633)	140.3+/-9.2 (332)	0.05
Serum Potassium Low				
	Mean +/-SD (n)	4.0+/-5.5 (634)	3.9+/-0.6 (332)	0.26
Serum Potassium High				

	Mean +/-SD (n)	4.7+/-6.1 (634)	4.6+/-2.8 (332)	0.06
White Blood Cell Count Low				
	Mean +/-SD (n)	12.8+/-25.1 (634)	12.5+/-8.6 (332)	0.15
White Blood Cell Count High				
	Mean +/-SD (n)	16.4+/-29.9 (634)	16.5+/-11.3 (332)	0.08
Pre-ICU Albumin				
	Mean +/-SD (n)	30.5+/-7.2 (432)	28.5+/-7.4 (330)	<0.001
Pre-ICU Hemoglobin				
	Mean +/-SD (n)	114.1+/-26.3 (893)	113.7+/-26.0 (516)	0.56

Appendix – Figure 2
Univariate Analysis for Medical Patients Using Cutpoints

	Total #		#Deaths/Total #	OR (95% CI)	P Value
Age	1028				0.05
		80-84	194/509 (38.1%)	Referent	
		85-89 vs. 80-84	177/398 (44.5%)	1.30 (1.00-1.70)	
		>90 vs. 80-84	58/121 (47.9%)	1.50 (1.00-2.23)	
Gender	1033				0.91
		Male	235/568 (41.4%)	Referent	
		Female	194/465 (41.7%)	1.01 (0.79-1.30)	
GCS	594				<0.0001
		15	71/262 (27.1%)	Referent	
		3 vs. 15	35/43 (81.4%)	11.77 (5.21-26.59)	
		4-8 vs. 15	54/85 (63.5%)	4.69 (2.79-7.87)	
		8-12 vs. 15	56/122 (45.9%)	2.28 (1.46-3.57)	
		13-14 vs. 15	32/82 (39.0%)	1.72 (1.02-2.90)	
Heart Rate High	593				0.001
		50-99	86/253 (34.0%)	Referent	
		100-139 vs. 50-99	131/281 (46.6%)	1.70 (1.20-2.41)	
		>139 vs. 50-99	33/59 (55.9%)	2.47 (1.39-4.38)	
Respiratory Rate	593				0.002
		10-20	37/114 (32.5%)	Referent	
		21-30 vs. 10-20	119/302 (39.4%)	1.35 (0.86-2.13)	
		31-40 vs. 10-20	75/149 (50.3%)	2.11 (1.27-3.50)	
		>40 vs. 10-20	18/28 (64.3%)	3.75 (1.57-8.91)	
Ever Received Vasoactive	1033				<0.0001

Medications					
		No	178/530 (33.6%)	Referent	
		Yes	251/503 (49.9%)	1.97 (1.53-2.53)	
pH	442				<0.0001
		>7.15	174/398 (43.7%)	Referent	
		<7.15 vs. >7.15	34/44 (77.3%)	4.38 (2.10-9.10)	
Serum Sodium High	577				0.12
		131-145	201/490 (41.0%)	Referent	
		146-150 vs. 131-145	27/65 (41.5%)	1.02 (0.60-1.73)	
		>150 vs. 131-145	14/22 (63.6%)	2.52 (1.04-6.11)	
Serum Potassium Low	570				0.06
		3.0-5.0	219/539 (40.6%)	Referent	
		<2.9 vs. 3.0-5.0	18/31 (58.1%)	2.02 (0.97-4.21)	
Serum Potassium High	590				0.07
		2.9-5.0	200/503 (39.8%)	Referent	
		5.0-6.5 vs. 2.9-5.0	40/75 (53.3%)	1.73 (1.06-2.82)	
		>6.5 vs. 2.9-5.0	6/12 (50.0%)	1.52 (0.48-4.76)	
Serum Creatinine High	594				<0.0001
		<120	101/290 (34.8%)	Referent	
		120-300 vs. <120	113/251 (45.0%)	1.53 (1.08-2.17)	
		>300 vs. <120	36/53 (67.9%)	3.96 (2.12-7.41)	
WBC Low	278				0.0009
		4.0-10.0	93/252 (36.9%)	Referent	
		<4.0 vs. 4.0-10.0	19/26 (73.1%)	4.64 (1.88-11.45)	
WBC High	583				0.13

		4.0-10.0	56/158 (35.4%)	Referent	
		10.1-20.0 vs. 4.0-10.0	126/297 (42.4%)	1.34 (0.90-2.00)	
		20.1-30.0 vs. 4.0-10.0	39/83 (47.0%)	1.61 (0.94-2.77)	
		30.1-40.0 vs. 4.0-10.0	8/25 (32.0%)	0.86 (0.35-2.11)	
		>40.0 vs. 4.0-10.0	12/20 (60.0%)	2.73 (1.05-7.08)	

Comparison of Medical Patients With and Without Complete Data

--where "complete" data refers to all of the Apache II components that were entered into the multivariable logistic regression analysis

Age

	All Patients (n=1033)	Patients with Complete Data (n=440)	Patients with Incomplete Data (n=593)
Age in years*	84.6+/-3.5	84.6+/-3.5	84.7+/-3.6
Age Range	79.9-100.2	79.9-99.4	79.9-100.2

Gender

	All Patients (n=1033)	Patients with Complete Data (n=440)	Patients with Incomplete Data (n=593)
Male (%)	568 (55.0%)	247 (56.1%)	321 (54.1%)

Primary ICU Diagnosis

Primary ICU Diagnosis	Patients with Complete Data (% of total)	Patients with Incomplete Data (% of total)
Cardiovascular / Vascular	86 (8.3%)	126 (12.2%)
Respiratory	174 (16.8%)	187 (18.1%)
Gastrointestinal	36 (3.5%)	38 (3.7%)
Neurologic	28 (2.7%)	86 (8.3%)
Sepsis	77 (7.5%)	94 (9.1%)
Trauma	11 (1.1%)	26 (2.5%)
Metabolic	7 (0.7%)	11 (1.1%)
Hematologic	20 (1.9%)	23 (2.2%)
Renal	0 (0.0%)	1 (0.1%)
Orthopedic	1 (0.1%)	1 (0.1%)
Total	440 (42.6%)	593 (57.4%)

Baseline Apache II

	All Patients (n=1033)	Patients with Complete Data (n=440)	Patients with Incomplete Data (n=593)
Apache II*	23.1 +/-7.9	24.9+/-7.5	21.7+/-7.9

Charleson Co-morbidity Index

	All Patients (n=1033)	Patients with Complete Data (n=440)	Patients with Incomplete Data (n=593)
Charleson Co-morbidity Index*	2.2+/-1.8	2.2+/-1.8	2.2+/-1.7

Functional Co-morbidity Index

	All Patients (n=1033)	Patients with Complete Data (n=440)	Patients with Incomplete Data (n=593)
Functional Co-morbidity Index*	**1.9+/-1.4**	**1.9+/-1.5**	**1.9+/-1.3**

Pre-ICU Albumin

	All Patients (n=479)	Patients with Complete Data (n=213)	Patients with Incomplete Data (n=266)
Pre-ICU Albumin(g/L)*	29.5+/-7.2	29.2+/-7.7	29.7+/-6.8

- 554 patients did not have a Pre-ICU Albumin recorded

Pre-ICU Hemoglobin

	All Patients (n=860)	Patients with Complete Data (n=383)	Patients with Incomplete Data (n=477)
Pre-ICU Hemoglobin (g/L)*	114.1+/-25.9	113.9+/-25.5	114.3+/-26.2

- 173 patients did not have a Pre-ICU Hemoglobin recorded

Baseline SOFA Score

	All Patients (n=1032)	Patients with Complete Data (n=440)	Patients with Incomplete Data (n=592)
Baseline SOFA Score*	5.3+/-3.4	6.0+/-3.3	4.7+/-3.4

*value +/- std deviation

Comparison of Surgical Patients With and Without Complete Data

--where "complete" data refers to all of the Apache II components that were entered into the multivariable logistic regression analysis

Age

	All Patients (n=418)	Patients with Complete Data (n=212)	Patients with Incomplete Data (n=206)
Age in years*	84.4+/-3.4	84.4+/-3.2	84.5+/-3.5
Age Range	80.0-96.6	80.0-96.6	80.0-95.4

Gender

	All Patients (n=418)	Patients with Complete Data (n=212)	Patients with Incomplete Data (n=206)
Male (%)	224 (53.6%)	247 (56.1%)	321 (51.0%)

Primary ICU Diagnosis

Primary ICU Diagnosis	Patients with Complete Data (% of total)	Patients with Incomplete Data (% of total)
Cardiovascular / Vascular	59 (27.8%)	25 (12.1%)
Respiratory	7 (3.3%)	5 (2.4%)
Gastrointestinal	87 (41.0%)	102 (49.5%)
Neurologic	28 (13.2%)	27 (13.1%)
Sepsis	1 (0.5%)	1 (0.5%)
Trauma	19 (9.0%)	18 (8.7%)
Renal	0 (0.0%)	3 (1.5%)
Orthopedic	11 (5.2%)	25 (12.1%)
Total	212 (50.7%)	206 (49.3%)

Baseline Apache II

	All Patients (n=418)	Patients with Complete Data (n=212)	Patients with Incomplete Data (n=206)
Apache II*	22.1 +/-7.2	23.4+/-7.4	20.8+/-6.9

Charleson Co-morbidity Index

	All Patients (n=418)	Patients with Complete Data (n=212)	Patients with Incomplete Data (n=593)
Charleson Co-morbidity Index*	1.9+/-1.9	1.7+/-1.9	2.1+/-2.0

Functional Co-morbidity Index

	All Patients (n=418)	Patients with Complete Data (n=212)	Patients with Incomplete Data (n=206)
Functional Co-morbidity Index*	1.7+/-1.4	1.5+/-1.3	1.8+/-1.5

Pre-ICU Albumin

	All Patients (n=188)	Patients with Complete Data (n=96)	Patients with Incomplete Data (n=92)
Pre-ICU Albumin(g/L)*	28.7+/-6.8	30.4+/-6.9	26.9+/-6.4

- 230 patients did not have a Pre-ICU Albumin recorded

Pre-ICU Hemoglobin

	All Patients (n=367)	Patients with Complete Data (n=193)	Patients with Incomplete Data (n=174)
Pre-ICU Hemoglobin (g/L)*	114.3+/-27.0	113.2+/-27.9	115.6+/-26.0

- 51 patients did not have a Pre-ICU Hemoglobin recorded

Baseline SOFA Score

	All Patients (n=418)	Patients with Complete Data (n=212)	Patients with Incomplete Data (n=206)
Baseline SOFA Score*	5.3+/-3.3	5.5+/-3.3	5.1+/-3.3

*value +/- std deviation

Hospital Mortality

	All Patients (n=418)	Patients with Complete Data (n=212)	Patients with Missing Data (n=206)
Hospital Mortality	132 (31.6%)	69 (32.6%)	63 (30.6%)

Appendix Figure 3: Multivariate Logistic Regression Analysis of Medical Patients

The SAS System
The LOGISTIC Procedure

Model Information	
Data Set	WORK.APACHESCORE
Response Variable	HospDie
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	436
Number of Observations Used	436

Response Profile

Ordered Value	*HospDie*	*Total Frequency*
1	1	208
2	0	228

Probability modeled is HospDie=1.

Class Level Information

Class	*Value*	*Design Variables*			
ageGrp	*80-84*	0	0		
	85-89	1	0		
	>90	0	1		
CreGrp	*120-300*	1	0		
	<120	0	0		
	>300	0	1		
GCSgrp	*13-14*	1	0	0	0
	15	0	0	0	0
	3	0	1	0	0

Class Level Information					
Class	Value	Design Variables			
	4-8	0	0	1	0
	8-12	0	0	0	1
PHgrp	<7.15	1			
	>7.15	0			
HRhigh_grpNEW	<120	0			
	>=120	1			

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	Intercept Only	Intercept and Covariates
AIC	605.507	536.651
SC	609.584	581.505
-2 Log L	603.507	514.651

R-Square	0.1844	Max-rescaled R-Square	0.2460

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	88.8553	10	<.0001
Score	80.3800	10	<.0001
Wald	65.6115	10	<.0001

Type 3 Analysis of Effects			
Effect	DF	Wald Chi-Square	Pr > ChiSq
ageGrp	2	8.8459	0.0120
CreGrp	2	18.2138	0.0001
GCSgrp	4	42.9506	<.0001

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
PHgrp	1	4.4452	0.0350
HRhigh_grpNEW	1	2.3911	0.1220

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	Label
Intercept		1	-1.6932	0.2676	40.0437	<.0001	Intercept: HospDie=1
ageGrp	*85-89*	1	0.4873	0.2305	4.4678	0.0345	ageGrp 85-89
ageGrp	*>90*	1	0.9707	0.3723	6.7971	0.0091	ageGrp >90
CreGrp	*120-300*	1	0.4504	0.2260	3.9710	0.0463	CreGrp 120-300
CreGrp	*>300*	1	1.6664	0.3963	17.6810	<.0001	CreGrp >300
GCSgrp	*13-14*	1	0.7349	0.3295	4.9747	0.0257	GCSgrp 13-14
GCSgrp	*3*	1	2.1939	0.4515	23.6099	<.0001	GCSgrp 3
GCSgrp	*4-8*	1	1.7497	0.3283	28.4101	<.0001	GCSgrp 4-8
GCSgrp	*8-12*	1	0.8355	0.2774	9.0743	0.0026	GCSgrp 8-12
PHgrp	*<7.15*	1	0.8925	0.4233	4.4452	0.0350	PHgrp <7.15
HRhigh_grpNEW	*>=120*	1	0.3700	0.2393	2.3911	0.1220	HRhigh_grpNEW >=120

Association of Predicted Probabilities and Observed Responses

Percent Concordant	73.1	*Somers' D*	0.482
Percent Discordant	25.0	*Gamma*	0.491
Percent Tied	1.9	*Tau-a*	0.241
Pairs	47424	*c*	0.741

Odds Ratio Estimates and Wald Confidence Intervals

Effect		Unit	Estimate	95% Confidence Limits	
ageGrp	*85-89 vs 80-84*	1.0000	1.628	1.036	2.558
ageGrp	*>90 vs 80-84*	1.0000	2.640	1.272	5.476
CreGrp	*120-300 vs <120*	1.0000	1.569	1.007	2.444
CreGrp	*>300 vs <120*	1.0000	5.293	2.434	11.510
GCSgrp	*13-14 vs 15*	1.0000	2.085	1.093	3.978
GCSgrp	*3 vs 15*	1.0000	8.971	3.702	21.735
GCSgrp	*4-8 vs 15*	1.0000	5.753	3.023	10.947

Odds Ratio Estimates and Wald Confidence Intervals					
Effect		*Unit*	*Estimate*	*95% Confidence Limits*	
GCSgrp	*8-12 vs 15*	1.0000	2.306	1.339	3.972
PHgrp	*<7.15 vs >7.15*	1.0000	2.441	1.065	5.597
HRhigh_grpNEW	*>=120 vs <120*	1.0000	1.448	0.906	2.314

Partition for the Hosmer and Lemeshow Test					
		HospDie = 1		*HospDie = 0*	
Group	*Total*	*Observed*	*Expected*	*Observed*	*Expected*
1	42	9	7.24	33	34.76
2	46	8	10.80	38	35.20
3	51	16	15.64	35	35.36
4	47	23	17.86	24	29.14
5	43	17	18.16	26	24.84
6	44	21	22.03	23	21.97
7	45	25	25.85	20	19.15
8	42	25	27.74	17	14.26
9	44	33	33.71	11	10.29
10	32	31	28.98	1	3.02

Hosmer and Lemeshow Goodness-of-Fit Test		
Chi-Square	*DF*	*Pr > ChiSq*
6.5061	8	0.5907

Appendix Figure 5: Multivariable Logistic Regression Data for Surgical Emergency Patients

The LOGISTIC Procedure

Model Information	
Data Set	WORK.APACHESCORE
Response Variable	HospDie
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	418
Number of Observations Used	212

Response Profile

Ordered Value	*HospDie*	*Total Frequency*
1	1	69
2	0	143

Probability modeled is HospDie=1.

Note: 206 observations were deleted due to missing values for the response or explanatory variables.

Class Level Information

Class	*Value*	*Design Variables*	
ageGrp	*<90*	0	
	>=90	1	
CreGrp	*120-300*	1	0
	<120	0	0
	>300	0	1
GCSgrp	*13-15*	1	0
	3-8	0	0
	9-12	0	1
PHgrp	*<7.15*	1	
	>7.15	0	

Class Level Information		
Class	Value	Design Variables
HRhigh_grp	<120	0
	>=120	1

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	Intercept Only	Intercept and Covariates
AIC	269.512	250.871
SC	272.869	281.081
-2 Log L	267.512	232.871

R-Square	0.1507	Max-rescaled R-Square	0.2103

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	34.6410	8	<.0001
Score	33.8392	8	<.0001
Wald	27.8369	8	0.0005

Type 3 Analysis of Effects			
Effect	DF	Wald Chi-Square	Pr > ChiSq
VasoReceived	1	1.9316	0.1646
ageGrp	1	1.8834	0.1700
CreGrp	2	14.2167	0.0008
GCSgrp	2	5.3561	0.0687
PHgrp	1	5.4919	0.0191
HRhigh_grp	1	2.5417	0.1109

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	Label
Intercept		1	-0.7857	0.4207	3.4882	0.0618	Intercept: HospDie=1
VasoReceived		1	0.5006	0.3602	1.9316	0.1646	
ageGrp	*>=90*	1	0.8810	0.6420	1.8834	0.1700	ageGrp >=90
CreGrp	*120-300*	1	1.0397	0.3558	8.5388	0.0035	CreGrp 120-300
CreGrp	*>300*	1	2.7929	0.9555	8.5436	0.0035	CreGrp >300
GCSgrp	*13-15*	1	-0.9426	0.4262	4.8917	0.0270	GCSgrp 13-15
GCSgrp	*9-12*	1	-0.8397	0.4555	3.3986	0.0653	GCSgrp 9-12
PHgrp	*<7.15*	1	1.7918	0.7646	5.4919	0.0191	PHgrp <7.15
HRhigh_grp	*>=120*	1	-0.6563	0.4117	2.5417	0.1109	HRhigh_grp >=120

Association of Predicted Probabilities and Observed Responses

Percent Concordant	71.4	*Somers' D*	0.483
Percent Discordant	23.1	*Gamma*	0.511
Percent Tied	5.4	*Tau-a*	0.213
Pairs	9867	*c*	0.742

Odds Ratio Estimates and Wald Confidence Intervals

Effect		Unit	Estimate	95% Confidence Limits	
VasoReceived		1.0000	1.650	0.814	3.342
ageGrp	*>=90 vs <90*	1.0000	2.413	0.686	8.493
CreGrp	*120-300 vs <120*	1.0000	2.828	1.408	5.680
CreGrp	*>300 vs <120*	1.0000	16.328	2.510	106.236
GCSgrp	*13-15 vs 3-8*	1.0000	0.390	0.169	0.898
GCSgrp	*9-12 vs 3-8*	1.0000	0.432	0.177	1.054
PHgrp	*<7.15 vs >7.15*	1.0000	6.000	1.341	26.851
HRhigh_grp	*>=120 vs <120*	1.0000	0.519	0.232	1.162

Partition for the Hosmer and Lemeshow Test

		HospDie = 1		*HospDie = 0*	
Group	*Total*	*Observed*	*Expected*	*Observed*	*Expected*
1	12	1	1.29	11	10.71
2	47	8	7.09	39	39.91
3	19	3	3.38	16	15.62
4	23	5	5.43	18	17.57
5	24	7	7.19	17	16.81
6	17	5	5.74	12	11.26
7	23	8	10.11	15	12.89
8	22	14	11.17	8	10.83
9	25	18	17.59	7	7.41

Hosmer and Lemeshow Goodness-of-Fit Test

Chi-Square	*DF*	*Pr > ChiSq*
2.7382	7	0.9081