

Award Number:  
W81-XWH-09-2-0175

TITLE:  
Proposal for Development of EBM-CDSS (Evidence-based Clinical Decision Support System) to  
Aid Prognostication in Terminally Ill Patients

PRINCIPAL INVESTIGATOR:  
Benjamin Djulbegovic, MD, PhD

CONTRACTING ORGANIZATION: University of Florida  
Tampa, FL 33612

REPORT DATE: October 2014

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: . \* Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

| REPORT DOCUMENTATION PAGE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                          | Form Approved<br>OMB No. 0704-0188           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|----------------------------------------------|
| <small>Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.</small> |                          |                                              |
| 1. REPORT DATE<br>October 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 2. REPORT TYPE:<br>FINAL | 3. DATES COVERED<br>25 Sep 2009- 24 Sep 2014 |
| 4. TITLE AND SUBTITLE<br>Proposal for development of EBM-CDSS (Evidence-based Clinical Decision Support System) to aid prognostication in terminally ill patients                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                          | 5a. CONTRACT NUMBER                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                          | 5b. GRANT NUMBER<br>W81-XWH-09-2-0175        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                          | 5c. PROGRAM ELEMENT NUMBER                   |
| 6. AUTHOR(S)<br><br>Benjamin Djulbegovic, MD, PhD<br><br>email: bdjulbeg@health.usf.edu                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                          | 5d. PROJECT NUMBER                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                          | 5e. TASK NUMBER                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                          | 5f. WORK UNIT NUMBER                         |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)<br><br>University of Florida<br>Tampa, FL 33612                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                          | 8. PERFORMING ORGANIZATION REPORT<br>NUMBER  |
| 9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)<br>U.S. Army Medical Research and Materiel Command<br>Fort Detrick, Maryland 21702-5012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                          | 10. SPONSOR/MONITOR'S ACRONYM(S)             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                          | 11. SPONSOR/MONITOR'S REPORT<br>NUMBER(S)    |
| 12. DISTRIBUTION / AVAILABILITY STATEMENT<br>Approved for Public Release; Distribution Unlimited                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                          |                                              |
| 13. SUPPLEMENTARY NOTES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                          |                                              |

**14. ABSTRACT**

Goal of the project is to develop an Evidence-based Clinical Decision Support (EBM-CDSS) system and make it available at the point of care to improve prognostication of the life expectancy of terminally ill patients to improve referral of patients to hospice. In addition, the EBM-CDSS will be expanded with an evidence based pain management module (EB-PMM) to assist physicians managing patients with pain. Currently, the study is being conducted at the Moffitt Cancer Center (MCC) and Tampa General Hospital (TGH). [Both sites received scientific review committee, IRB and the sponsor approval]. So far our key research accomplishments are as follows: we

- We identified research associates (one at each study site) to serve as a back-up for our current research associates to interview patients, collect data and manage the study related activities.
- We designed the Spanish version of the informed consent forms for our study. A certified translator translated the original English language informed consent forms into Spanish language.
- We have actively worked with IRB, physicians, nurses and physicians assistants at both MCC and TGH to inform them about the study and listened their suggestions how to improve it including the patient enrollment into the study.
  - To date, we have enrolled 127 study participants [we have screened and approached 807 patients]
  - Obtained approval from the USF Institutional Review Board for the amendments.
  - Actively monitoring all aspects of the study.
  - Refined our evidence based pain management module and developed a version of evidence based pain management module to make it available on the mobile platforms.
  - Published three manuscripts for peer-reviewed publication and one meeting abstract were accepted for an oral presentation at a prestigious national meeting.
  - Submitted the no cost extension application.

**15. SUBJECT TERMS-**

CDSS, SUPPORT, DEALE, Terminally ill, Hospice, Prognostication

**16. SECURITY CLASSIFICATION OF:**

**a. REPORT**  
U

**b. ABSTRACT**  
U

**c. THIS PAGE**  
U

**17. LIMITATION  
OF ABSTRACT**

UU

**18. NUMBER  
OF PAGES**

41

**19a. NAME OF RESPONSIBLE PERSON**  
USAMRMC

**19b. TELEPHONE NUMBER** *(include area code)*

| <b>Table of contents</b>     |             |
|------------------------------|-------------|
|                              | Page number |
| Introduction                 | 5           |
| Key Research Accomplishments | 5           |
| Reportable Outcomes          | 7           |
| Conclusion                   | 8           |
| Next steps                   | 9           |
| Appendices                   | 12          |

## Introduction

The goal of this project is to develop an Evidence-based Clinical Decision Support System (CDSS-EBM) available at the point of care which will improve prognostication of life expectancy of terminally ill patients and facilitate the hospice referral process. In addition, the CDSS-EBM will be expanded with an evidence based pain management module (EB-PMM) to assist physicians managing patients with pain.

## Body:

### Key research-related accomplishments (since the submission of previous annual progress report):

Currently, the study is being conducted at the Moffitt Cancer Center (MCC) and Tampa General Hospital (TGH).

We have submitted the no cost extension application.

Our progress regarding the task outlined in the statement of work is as follows:

Task 5: Implementation of EBM-CDSS to calculate life expectancy and referral decision thresholds using decision curve analysis (DCA) and acceptable regret (ARg) models

- At the TGH site we have screened 636 participants for eligibility and enrolled a total of 88 study participants. At the MCC site we have screened 171 individuals and have enrolled 39 study participants.
- We identified research associates (one at each study site) to serve as a back-up for our current research associates to interview patients, collect data and manage the study related activities at our MCC and TGH sites.
- We completed the training of the new research associates regarding EBM-CDSS software and data collection procedures. This step was essential to continue the prospective phase of our study at our study sites i.e. to enable continuing enrollment patients when our RAs are on vacation, or call in sick etc.
- As a result, we submitted an amendment to the University of South Florida (USF) Institutional Review Board to request to include these individuals to the study and obtained the approval for this request.
- We invested significant amount of time in training the new research associates in using the EBM-CDSS software and fine tuning their interviewing skills.
- We designed the Spanish version of the informed consent forms for our study. A certified translator translated the original English language informed consent forms into Spanish language. This lends credibility to the translated version of the consents

ensuring that the consents have the same content as the English language. We also submitted the official certificate of translation. We obtained an approval for these translated documents from the USF Institutional Review Board.

- We conducted a number of meetings with MCC and TGH physicians and presented our research study. These meeting were fruitful; especially in establishing trust and working relationship with MCC physicians which was also evident by inclusion of our study as part of the MCC clinical trials flow software. This will boost the number of patients referred by MCC physicians for participation in our study. Specifically, the PI and research coordinators have given a number of presentations to the referring physicians, social workers, nurses and staff at Moffitt and TGH to educate them on the study as well as ways that they can help with the referral process. This helped the awareness with the study in the Thoracic Clinic, Head and Neck Clinic and the Senior Adult Oncology Program at MCC as well as Palliative Care at TGH.
- We have met with the number of the key physicians and their teams (and continue to meet) to explain the purpose of the study. This will be continuing effort on our part as the study cannot succeed without adequate referrals from the physicians at MCC and TGH.
- We have used various strategies to raise awareness of our study to the referring physicians from the various specialties at MCC and TGH in order to improve enrollment of the patients in the prospective phase of our study. As a result recruitment has been expanded to include the Head and Neck cancers program in addition to senior adult oncology, sarcoma, malignant hematology, gastrointestinal, and thoracic oncology programs.
- We have refined our Evidence-based Chronic Pain Management Module to complement the CDSS-EBM. Our objective is to develop a reliable dosage conversion system as well as a knowledge base for each available pain medication. We have also incorporated evidence profiles for each drug to support the decision making using our pain management module.
- We have designed and developed two different versions of the pain module. The first version is accessible through the web by any computer with internet access and the second is optimized to be used on mobile iPad devices. Both versions of the pain module are guided by the National Comprehensive Cancer Network (NCCN) guidelines and include medication evidence profiles that we have generated. In addition, we have created test cases that will be used to test our applications first in house and then with our collaborators before full deployment.
- We have also created a survey to test usefulness of EB-PMM its users. The system went through the final programming phase and it will be first tested internally and then in the

clinic in the prospective phase of the study. We have also created the users manual for the EB-PMM.

- The iOS (Ipad) based version of our EBM-PMM is designed to assist physicians manage pain in adult cancer patients. The application includes the following functionalities:
  - Pain screening with standardized pain rating scale used to determine the patient's level of pain;
  - Selection of the appropriate medication based on to the levels of pain, type of patient (opioid naïve or opioid tolerant) and patient's preferences;
  - Calculation of total daily dose and single dose according to the medication presentation/concentration.
  - Conversion or rotation from one opioid to another opioid medication.
  - Prescription generation.

We plan to test the usability and functionality of the application in our clinical sites.

- Published three manuscripts in peer-reviewed journals and one meeting abstract was accepted for an oral presentation at a prestigious national meeting.

## Reportable outcomes

### 1. Publications so far:

- Eleazar Gil-Herrera, Ali Yalcin, Athanasios Tsalatsanis, Laura E. Barnes and Benjamin Djulbegovic, "Towards a Classification Model to Identify Hospice Candidates in Terminally Ill Patients", to appear in the Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2012
- Miladinovic B, Kumar A, Mhaskar R, Kim S, Schonwetter R, et al. (2012) A Flexible Alternative to the Cox Proportional Hazards Model for Assessing the Prognostic Accuracy of Hospice Patient Survival. PLoS ONE 7(10): e47804. doi:10.1371/journal.pone.0047804
- A. Tsalatsanis, I. Hozo, A. Vickers, B. Djulbegovic, "A regret theory approach to decision curve analysis: A novel method for eliciting decision makers' preferences and decision-making", BMC Medical Informatics and Decision Making 2010, 10:51 (16 September 2010)
- A. Tsalatsanis, L. Barnes, I. Hozo, B. Djulbegovic, "Extensions to Regret-based Decision Curve Analysis: An Application to hospice referral for terminal patients", BMC Medical Informatics and Decision Making 2011, 11:77 (23 December 2011)
- E. Gil-Herrera, A. Yalcin, A. Tsalatsanis, L. Barnes, B. Djulbegovic, "Rough set theory based prognostication of life expectancy for terminally ill patients", Proceedings of the IEEE EMBC 2011

- Mhaskar R, Miladinovic B, Tsalatsanis A, Mbah A, Kumar A, Kim S, Schonwetter R, Djulbegovic B. External Validation of Prognostic Models in Terminally Ill Patients. In: Hematology ASO, editor. American Society of Hematology Annual Conference; San Diego, California, 2011
  - Wao H, Mhaskar R, Kumar A, Miladinovic B, Djulbegovic B. Survival of patients with non-small cell lung cancer without treatment: a systematic review and meta-analysis. *Systematic reviews*. 2013; 2(1): 10.
  - Miladinovic B, Mhaskar R, Kumar A, Kim S, Schonwetter R, Djulbegovic B. External validation of a web-based prognostic tool for predicting survival in patients in hospice care. *Journal of Palliative Care*, 2013.
2. Journal publications since last progress report: (appendix 1)
- Hernandez JM, Tsalatsanis A, Humphries LA, Miladinovic B, Djulbegovic B, Velanovich V. Defining optimum treatment of patients with pancreatic adenocarcinoma using regret-based decision curve analysis. *Annals of surgery*. 2014;259(6):1208-14. Epub 2013/10/31
  - E. Gil-Herrera, A. Tsalatsanis, A. Kumar, R. Mhaskar, A. Yalcin, B. Djulbegovic, "Identifying homogeneous subgroups for individual patient meta-analysis based on rough set theory", in proceedings of the IEEE Annual International Conference of EMBS, Chicago, Illinois, 2014.
  - A. Tsalatsanis, I. Hozo, B. Djulbegovic, "Empirical evaluation of the acceptable regret model of medical decision making" (oral presentation). Annual Meeting of Society for Medical Decision Making, Miami, Florida, Oct 18-22, 2014.
  - Pathak EB, Wieten S, Djulbegovic B. From hospice to hospital: short-term follow-up study of hospice patient outcomes in a US acute care hospital surveillance system. *BMJ open*. 2014; 4(7):e005196. Epub 2014/07/24.

## Conclusions

We have already completed the majority of tasks described in the statement of work. We believe that we have closely followed the grant's timeline where we could control the work process. At this point, we are focusing on enhancing enrollment of patients in our study and testing our Pain Decision Support System. The adequate patient accrual and empirical testing of Pain Decision Support is a key to the success of this project. We estimate that we would need to accrue at least 50-60 more patients for reliable statistical analysis. To accomplish this, we would need another year to complete the project. We have applied for NCE (no cost extension to allow us to complete the project and achieve sound scientific goals of the study). PI will

continue to carefully monitor the “situation on the ground” and further allocate distribution of the effort among the faculty and the staff from the available grant support to match the stated goals of our application.

## Next Steps

- Our immediate and most important next step is to continue enrollment of patients in the prospective phase of the study. This requires tackling and coordinating multiple logistical, regulatory and administrative issues, which so far we have been successfully addressing.
- We will continue to work very closely with TGH palliative team and team of co-investigators from MCC to accomplish the goals of the study.
- We will maintain the quality assurance and oversight necessary for successful execution of the study.
- The key next steps for the Decision Support System include:
  - Generation of evidence tables regarding treatment of each of the conditions identified in our prediction model.
  - Incorporation of the generated evidence in the calculations of survival probabilities that is expected to lead to better informed decisions.
  - Incorporation of the pain module into the main decision support system.
  - Design and development of the mobile version of the decision support system that will run on iPad devices.
- Key steps for our evidence based pain management module include:
  - Updates on the workflows based on latest NCCN guidelines
  - Generation of patient profiles
  - Testing cycle that includes an iterative process of in-house testing and updates based on testing feedback
  - General testing cycles with our collaborators and updates based on testing feedback
  - Full deployment

- Given accumulated experience to date, we have undertaken three systematic reviews aiming to synthesize existing research evidence in the literature to provide best evidence for informed decision-making in the end-of life setting. We have finalized the protocols and have collected the relevant studies to be included in these systematic reviews. We are in the data analysis and manuscript writing phase for all systematic reviews, shortly described below.

### **A Systematic Review of Prognostic Models for Survival among Patients near the End of Life**

The decision to forgo curative-intent medical treatments and enroll in hospice is a difficult choice faced by terminally-ill patients and their families. There are a number of prognostic models that have been developed to help clinicians counsel their patients about the best course of action, based on calculations of expected life expectancy and/or survival probabilities. So far, we have evaluated several of the most promising models. As reported before, some of these models did not perform well in our hands, while more promising ones were elected for testing in a prospective phase. In the meantime, several new models have been published in the literatures that look promising. Before incorporating these new models in the prospective phase of our project, we have elected a rigorous systematic review of these various models to determine which one deserve further testing in a prospective phase of the projects. Therefore, we have undertaken a comprehensive systematic review, focused on studies which were published during 2009-2014.

### **A Systematic Review of Studies of Beliefs about End of Life Health Care in the United States**

In the United States today, there is a growing emphasis on "patient-centered" health care (Hickam 2013). Proponents define "patient-centered" as health care which gives primacy to patient preferences in guiding medical decision making and the course of health care. Patient preferences can be in reference to the process of care (e.g. medical vs. surgical management), and/or to the outcomes of care (e.g. desire for self-ambulation vs. desire for complete pain control after a procedure) (Hickam 2013). Our experience to date has re-enforced the importance of understanding the differences among patients, their families and caregivers, and their health care providers in beliefs and attitudes toward end of life care. Researchers need to take every possible measure to respect the values and wishes of study participants. In 1997, the Institute of Medicine published a landmark report titled "Approaching Death: Improving Care at the End of Life." (Field 1997) Since that time, many small studies have been conducted which focus on either patient (e.g. Wicher 2012), health care provider (e.g. Ramalingam 2013) or caregiver (e.g. Oliver 2013) beliefs about end of life health care. However, there have been no comprehensive systematic reviews on this very important topic.

Our team has undertaken a comprehensive systematic review, focused on United States studies for which were published during 1998-2013, to capture the period after the release of the IOM report.

Of note, our accumulated experience with decision-making in the end-of-life setting has helped us generate new model for medical-decision making based on dual processing theory, which takes into account analytical as well as emotional, intuitive processes (see Appendix).

### **Palliative Care versus Disease-Targeted Management for Terminally Ill Adults: A Systematic Review and Meta-Analysis**

The number of people dying as a result of terminal illness in the United States is increasing (Seale 2000) with cancer and cardiovascular disease being a major cause of death, claiming 580,350 and 787,931 lives annually (American Cancer Society 2013; Go 2013). Despite the prevalence of 'predictable' deaths, it is not clear if patients with terminal illness stand to benefit or are harmed by continued aggressive disease-targeted management (DTM) as opposed to palliative care (PC). Despite the benefits to QOL which PC can provide, many patients continue to opt for DTM. Around 40% of patients with advanced lung cancer continued aggressive therapy through the final month of life (Temel 2008). Overall, around over 60% of cancer patients receive aggressive DTM within the last three months of life (Braga 2007; Martoni 2007; Keam 2008; Soh 2012). Over time, the number of patients receiving aggressive therapy within the last month of life has risen (Gonsalves 2011).

In contrast, some studies show a lack of survival benefit and increased adverse events associated with aggressive DTM in terminally ill patients (von Gruenigen 2008; Saito 2011; Temel 2010). Moreover, PC alone approach was associated with longer overall survival among patients with congestive heart failure, lung cancer, and pancreatic cancer (Connor 2007). Additionally, greater patient satisfaction, fewer hospital and intensive care admissions, and lower overall health care costs is associated with use of interdisciplinary PC team compared to standard DTM (Costantini 2003; Gade 2008). Three prospective studies showed that patients in PC, as opposed to aggressive treatment (Doubek 2005) or curative resection (Smoot 2008) or surgery/chemoradiation (Roh 2008) have a shorter median survival time. Providing the best evidence on the role of PC vs. DTM is one of the key ingredients of our EBM decision-support system. The "gold standard" methodology to provide and, importantly, update such evidence is to employ a technique of systematic review, and if applicable, followed by meta-analysis. (We will apply both traditional meta-analytic techniques as well as the one based on rough-set theory, which we recently developed. The application of rough set theory is directly informed by our use of this technique in this project so far; Appendix 2).

To date, no systematic review has assessed whether use of PC versus DTM in management of terminally ill patients has an impact on survival and QOL. While studies comparing PC versus DTM exist (Casarett 2001; Connor 2007; Costantini 2003; Gade 2008; Lewin 2005; Temel 2010), we are not aware of a systematic review and meta-analysis of such studies.

Therefore, we are conducting a systematic review to compare benefits and harms of palliative care versus disease-targeted management for the management of adults with terminal illness. In parallel, we are continuing to generate evidence tables from the ongoing literature search about the effects of DTM in the end of life setting. The results of this systematic review will be used to update evidence in our decision-support system.

## **Appendix 1 Peer-reviewed journal publications**

### **Defining Optimum Treatment of Patients with Pancreatic Adenocarcinoma using Regret-based Decision Curve Analysis**

Running Title: Regret Decision Analysis in Pancreatic Cancer

Jonathan M. Hernandez MD<sup>1</sup>, Athanasios Tsalatsanis PhD<sup>2,3</sup>, Leigh Ann Humphries<sup>1</sup>,  
Branko Miladinovic PhD<sup>2,3</sup>, Benjamin Djulbegovic MD Ph.D.<sup>2,3,4</sup>, Vic Velanovich MD<sup>1\*</sup>

<sup>1</sup>Department of Surgery, Division of General Surgery, University of South Florida Tampa, FL, USA

<sup>2</sup>Center for Evidence Based Medicine, University of South Florida, Tampa, FL, USA

<sup>3</sup>Department of Internal Medicine, Division of Evidence-based Medicine, Tampa, FL, USA

<sup>4</sup>Department of Hematology and Health Outcomes and Behavior, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA

All authors declare that they have no conflicts of interest.

\*Corresponding Author:

Vic Velanovich, MD

Department of General Surgery

1 Tampa General Circle, F145

Tampa, FL 33606

vvelanov@health.usf.edu

## ABSTRACT

**Background:** Pancreatic adenocarcinoma is uniformly fatal without operative intervention. Resection can prolong survival in some patients; however, it is associated with significant morbidity and mortality. Regret theory serves as a novel framework linking both rationality and intuition to determine the optimal course for physicians facing difficult decisions related to treatment.

**Methods:** We used the Cox proportional hazards model to predict survival of patients with pancreatic adenocarcinoma and generated a decision model using regret-based decision curve analysis, which integrates both the patient's prognosis and the physician's preferences expressed in terms of regret associated with a certain action. A physician's treatment preferences are indicated by a threshold probability, which is the probability of death/survival at which the physician is uncertain whether or not to perform surgery. The analysis modeled three possible choices: perform surgery on all patients, never perform surgery, and act according to the prediction model.

**Results:** The records of 156 consecutive patients with pancreatic adenocarcinoma were retrospectively evaluated by a single surgeon at a tertiary referral center. Significant independent predictors of overall survival included preoperative stage ( $p=0.005$ , CI 1.19-2.27), vitality ( $p<0.001$ , CI 0.96-0.98), daily physical function ( $p<0.001$ , CI 0.97-0.99) and pathologic stage ( $p<0.001$ , CI 3.06-16.05). Compared with the "always aggressive" or "always passive" surgical treatment strategies, the survival model was associated with the least amount of regret for a wide range of threshold probabilities.

**Conclusions:** Regret-based decision curve analysis provides a novel perspective for making treatment-related decisions by incorporating the decision maker's preferences expressed as his/her estimates of benefits and harms associated with the treatment considered.

## INTRODUCTION

Although significant progress has been made over the last two decades in reducing perioperative mortality for patients with localized pancreatic adenocarcinoma, pancreaticoduodenectomy remains associated with significant morbidity(1, 2). Moreover, long-term survival has remained unchanged and persistently elusive for the vast majority of patients with the disease(3, 4). Operative extirpation, for which about 15-20% of patients are eligible, is undertaken when technically feasible because it offers the only opportunity for prolonged survival, and because there are few alternative treatments – each of which has limited efficacy(5). However, even among patients undergoing complete tumor extirpation with negative margins, the disease recurs in 40% of the patients within 6 months, most commonly in the form of liver metastasis (6). These patients may derive little-to-no survival benefit from local control, while potentially suffering from operative morbidity(6). Selection of patients likely to benefit from aggressive local control is therefore particularly important in the management of patients with radiographic-localized pancreatic adenocarcinoma.

Decision analysis typically defines the probability of an event and provides the optimal model among alternative clinical management strategies, thus maximizing a definable outcome (7, 8). Probability models based on diagnostic and prognostic variables have been utilized to assist physician decision-making regarding various treatments and interventions, including resection for cancer, although the effectiveness of the models remains questionable(9-15). The reasons behind this skepticism include the probabilistic nature of these models that adds complexity to the decision process and, importantly, the reliance of most of these models on expected utility theory, which is often violated during decision making(16-20).

We recently developed a decision methodology that overcomes the limitations of probabilistic survival models, and which can be utilized to facilitate medical decisions based on the decision-maker preferences (19, 20). Our methodology, Regret-based Decision Curve Analysis or *Regret DCA*, relies on the cognitive emotion of regret to identify conditions under which a physician is unsure about the choice between alternative treatment strategies (19, 20). Surgeons, as with any decision maker, may experience regret (defined as the difference between the utility of an action taken and utility of an alternative action) if they eventually realize that a decision they made was suboptimal, and that an alternative form of treatment would have been preferable (21-27). Regret DCA utilizes this regret to compute the threshold probability at which the physician is uncertain about which treatment strategy to recommend to his/her patient. In this study, we used Regret DCA to facilitate treatment decisions for a cohort of patients with localized, resectable pancreatic adenocarcinoma.

The intention of this article is to present a novel decision methodology that relies on regret theory and attempts to explain medical decision-making for surgeons treating patients with pancreatic adenocarcinoma. Despite the fact that the prediction model presented has been well fitted to our data, its role in this article is secondary and its purpose is to demonstrate how the regret methodology can be used to evaluate three management strategies: aggressive, passive, or model-based decision making. In this context, we have demonstrated that the prediction model performs better than the other two strategies in terms of regret.

## MATERIALS AND METHODS

The records of 156 consecutive patients referred for surgical consultation from January 2005 to 2009 with pancreatic adenocarcinoma were retrospectively reviewed by a single surgeon at a tertiary referral center. The diagnosis was confirmed by histological evaluation, and disease stage was determined by pathological evaluation of the resected specimen and by imaging. All patients had been administered the SF-36 Health Survey to assess quality of life, which includes 36 statements grouped into 8 domains of quality of life: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. The SF-36 utilizes a Likert scale of 0 to 100, with higher scores indicating better/normal health or physical functioning. We previously demonstrated that the SF-36 correlates well with pathology, survival, stage and resectability of pancreatic lesions (27).

The distribution for overall survival was estimated using the Kaplan-Meier Method. Cox proportional hazards modeling was used to determine the effect on survival of the following 12 covariates, including those described by SF-36: age, gender, stage, adjuvant therapy, physical functioning, role-physical, role-emotional, bodily pain, pretreatment vitality, mental health, social functioning and general

health. Additional covariates such as tumor characteristics (lymphovascular invasion, perineural invasion, etc.) could potentially influence the output of the Cox model, however, this information is typically unknown to the surgeon *a priori*. Furthermore, such covariates were not included in the analysis since our dataset was originally constructed based on the methods and protocols designed for a study (28) focusing on the quality of life, pathology, resectability and survival in patients with pancreatic lesions. The model was created using stepwise elimination on all variables ( $p < 0.15$  to enter, and  $p < 0.20$  to stay). The proportional hazards assumption was examined using Schoenfeld residuals. The importance of each variable and the discriminative ability of the Cox model was examined using Royston-Sauerbrei's discrimination statistic D and explained variation  $R^2_D$  (29). All continuous variables were centered about the mean. All analyses were performed using STATA (30).

To derive the optimal treatment strategy, we then utilized the Regret-based Decision Curve Analysis methodology (*Regret DCA*) (19, 20). Regret DCA employs the decision maker's feeling of regret to compute the threshold probability at which he/she is uncertain about alternative actions, e.g., to operate or not to operate. In considering decisions for patients with pancreatic adenocarcinoma, we considered survival less than 7 months from the time of tumor extirpation as being unlikely to have imparted a survival advantage, and therefore unnecessary based upon median survival of patients with locally advanced, non-metastatic disease (31). Based on this assumption, we formulated a decision model that compares an individual patient's prognosis with the threshold probability at which the surgeon would be indifferent about recommending surgery.

Typically, decision theory suggests that a person should be treated if the probability of an event (i.e. the patient develops a disease; the patient dies; the patient survives longer than a predefined timeframe, etc.) is greater than or equal to a threshold probability (7, 8, 32). In this paper, we sought to treat the patients who were likely to survive longer than 7 months from the time of their resection. Therefore, the convention used is: **if the patient's probability of surviving 7 months is greater than or equal to the threshold probability ( $s \geq P_t$ ), the surgeon should offer resection. If the patient's probability of survival is less than the threshold probability ( $s < P_t$ ), the patient may be unlikely to benefit substantially from surgery and the surgeon should not recommend resection in favor of medical alternatives.**

The probability of survival can be computed for each patient based on the Cox survival model previously described. However, the threshold probability is subject to each surgeon's preferences and clinical practice attitudes. At the individual level, it can be computed as (19, 20):

$$P_t = \frac{1}{1 + \frac{\text{Regret of omission}}{\text{Regret of commission}}} \quad (1)$$

We define "regret of omission" as the regret felt by a surgeon who withheld necessary surgery from a patient who may have benefited from that resection (patients with localized disease who lived longer than 7 months). Conversely, "regret of commission" is the regret felt by a surgeon who performed an unnecessary surgery on a patient who derived no benefit from that operation (e.g. the patient died as a result of the procedure or died within 7 months from the time of resection). Both regret values can be determined using the Dual Visual Analogue Scales (DVAs) (Figure 1) (19, 20). Formally, regret can be expressed as the difference between the utility of the outcome of an action taken and the utility of the outcome of the action that, in retrospect, should have been taken (21-27). Commonly used techniques for estimating utility, and therefore decision maker preferences, such as standard gamble and time trade-off are time consuming, cognitively complex and have been shown to lead to biased estimates of people's preferences (33-35). Instead, in this paper, we use the Dual Visual Analogue Scales (DVAs) to estimate directly the values of regret of commission and omission (19, 20). The DVAs comprise two 100-point scales, each anchored to no regret and maximum regret. One of the scales is used to elicit regret of omission and the other to elicit regret of commission (Figure 1).

After computing the surgeon's threshold probability, the clinical question regarding treatment for patients with pancreatic adenocarcinoma can be broken down into three strategies: 1. surgeons can stay passive and allow the disease to run its course, 2. surgeons can be aggressive and recommend resection on all patients, or 3. surgeons can use prediction model for guidance. Any of these strategies may cause regret if the outcome is poor. Under the Regret DCA methodology, the optimal strategy is the one that will cause

the least amount of regret if that strategy is proven suboptimal. Formally, regret can be expressed as the difference between the utility of the outcome of the action taken and the utility of the outcome of the action that, in retrospect, should have been taken (21-27). Considering the decision tree that describes this clinical problem (Figure 2), we can compute the expected regret associated with each of the three strategies as follows:

$$ERg[NoSurgery] = (1 - s) * \frac{P_t}{1 - P_t} \quad (2)$$

$$ERg[Surgery] = s \quad (3)$$

$$ERg[Model] = \frac{\#FP}{n} * \frac{P_t}{1 - P_t} + \frac{\#FN}{n} \quad (4)$$

The values of #FP and #FN correspond to the number of false positive and false negative results, respectively, as compared to the actual patient outcomes used for the development of the prediction model, and the number of patients in the dataset is  $n$ . We define true positive (TP), true negative (TN), false positive (FP), and false negative (FN) results as follows:

*TP*: the number of patients who will survive longer than 7 months and for whom the estimated probability of survival is greater than or equal to the threshold probability (i.e., the patients who should receive surgery).

*TN*: the number of patients who will die in 7 months and for whom the estimated probability of survival is less than the threshold probability (i.e., the patients who should NOT receive surgery).

*FP*: the number of patients who will die within 7 months and for whom the estimated probability of survival is greater than or equal to the threshold probability (i.e., the patients who received unnecessary surgery).

*FN*: the number of patients who will survive longer than 7 months and for whom the estimated probability of survival is less than the threshold probability (i.e., the number of patients who should have received surgery but did not).

As shown in equations 2 and 4, the expected regret associated with each strategy is a function of the physician's threshold probability. To identify the least regretful action, the Regret DCA methodology computes the expected regret for a range of threshold probabilities (0-100), and expected regret is then graphed against the threshold probability for each of the three actions. The action with the lowest value of expected regret corresponds to the most desired action, given a certain threshold probability.

## RESULTS

### *Patient Characteristics*

A total of 156 patients with histologically-confirmed primary pancreatic adenocarcinoma were included. The mean age was  $65.9 \pm 10$  years, 83% were stage I or II, 54% were resected, 66% received chemotherapy, and the median survival was 18 months (95% CI 12-26) (mean survival was  $15.7 \pm 25$  months). The SF-36 scores revealed that role-physical and pretreatment vitality had the lowest scores, and mental health had the highest score (Table 1). The distribution of overall survival is presented in Figure 3.

### *Survival model*

Of the 12 variables included in the dataset, three met the stepwise inclusion criteria and were used to construct the survival model: stage, pretreatment vitality, and role-physical (daily physical functioning). The explained variation of the fitted model was  $R^2_D = 0.4$  (95% CI: 0.27-0.52) and the proportional hazard assumption were not violated ( $P < 0.96$ ). Table 2 presents the estimates of hazard ratio for the Cox prediction model.

### *Regret Decision Curve Analysis*

We employed Regret DCA to evaluate the three management strategies: 1. Recommend against potentially curative surgery in favor chemotherapy or chemoradiotherapy; 2. be aggressive and recommend resection, 3. use the prediction model as a decision aid. Figure 4 depicts the expected regret as a function of threshold probability for each of the three management strategies. As shown, the least regretful strategy for threshold probabilities greater than 5% is to utilize the prediction model. For threshold probabilities between 80-87%, the regret curve associated with the prediction model is subject to noise (36) that we attribute to the error term of the Cox prediction model. We assume that the prediction model remains the least regretful

strategy within the 80-87% range as well. Our results demonstrate that the survival model we describe has significant clinical value for the majority of decision makers.

### **Hypothetical Case Study**

A 72 year-old female with diabetes and hypertension has been diagnosed with pancreatic adenocarcinoma after undergoing endoscopic retrograde cholangiopancreatography (ERCP) and common bile duct stenting for obstructive jaundice. She is currently without pain and is tolerating a regular diet. Her jaundice resolved after the placement of her biliary stent. Her CT scan demonstrates a localized mass in the head of the pancreas without involvement of the superior mesenteric vein, portal vein, superior mesenteric artery, or hepatic arteries. The patient is active and able to perform all activities of daily living. She expresses a strong desire to spend as much time as she can with her grandchildren.

We demonstrate the decision process assuming two types of hypothetical decision makers: One surgeon is extremely selective in offering resection to patients with pancreatic adenocarcinoma (Surgeon #1), and the second surgeon (Surgeon #2) generally offers resection to all patients with radiographically-resectable disease. The process, depicted in Figure 5, is initiated with the elicitation of the surgeon's preferences. Using the DVAS method (Figure 1) we estimate the threshold probability as a function of regret of omission and regret of commission (equation 1). Suppose that the answers to the questions shown in Figure 1 for the surgeons are as follows:

*Surgeon #1:* Regret of omission: 20; regret of commission: 90. Therefore, the threshold probability is equal to: 81.8% (equation 1).

*Surgeon #2:* Regret of omission: 90; regret of commission: 4. Therefore, the threshold probability is equal to: 4.2%.

Based on the results of Regret-DCA (Figure 4), the optimal and least regretful strategy for Surgeon#1 is to use the prognostication model we developed, described above. If the patient's estimated probability of survival is greater than or equal to 81.8% (the threshold for Surgeon #1) then the optimal strategy is to treat (perform the operation). If the probability of survival is less than 81.8%, then the optimal strategy is to offer alternative treatments (forego resection). Conversely, for Surgeon #2, whose threshold probability is equal to 4.2%, the optimal and least regretful strategy is to offer resection.

As mentioned earlier, the Regret-DCA methodology can also be used by the patients (19). For completeness, we present how this process could work. The patient would be asked questions similar to those depicted in Figure 1. We have previously shown that patient ratings of utility scores closely correlate with quality of life after pancreaticoduodenectomy; moreover, this patient-centered assessment may change over time as quality of life improves (37).

*Regret of omission:* On a scale of 0 to 100, where 0 = no regret and 100 = maximum regret you could feel, how would you rate your level of regret if you did not have an operation that could have extended your life?

*Regret of commission:* On a scale of 0 to 100, where 0 = no regret and 100 = maximum regret you could feel, how would you rate your level of regret if you had an operation that did not extend your life?

## **DISCUSSION**

We describe the theory and application of regret decision curve analysis as it applies to surgeons and to decisions regarding operative intervention in patients with pancreatic adenocarcinoma. To the best of our knowledge, this is the first application of regret DCA to assist surgeons in decision-making for patients with pancreatic malignancies. Our approach promotes personalized patient care by incorporating decision-maker preferences from the perspective of regret by estimating a threshold probability for a decision maker. We believe the decision regarding resection for patients with pancreatic adenocarcinoma is particularly well suited for a regret-based approach given the generally fatal prognosis for this disease, regardless of the decision made.

Modern cognitive theories seek to balance risks and benefits in the decision-making process by taking into account both intuition and analytical processes (37). We believe that rational decision-making

should take into account both the formal principles of rationality and human intuition. We have accomplished this using regret, a cognitive emotion, to serve as the link between intuition and analytical thinking (19, 20). Eliciting surgeons' preferences by using regret is likely to prove superior to using traditional utility theory because regret explicitly forces the surgeon to consider consequences of decisions. Our method relies on elicitation of a threshold probability, which must be calculated for every decision maker. In other words, our model forces surgeons to consider the possible outcomes of recommending pancreaticoduodenectomy rather than simply recommending resection for all tumors that appear resectable on radiographic imaging.

We argue that our approach contributes to the field of decision-making, but we acknowledge that it is not a panacea. We do, however, believe that our methodology is best suited for medical decision-making primarily associated with trade-offs between quality and quantity of life. Pancreatic adenocarcinoma meets this criterion: surgical resection may offer an additional year of survival, albeit with the potential for serious morbidity, particularly if the resection is undertaken at low-volume centers (38, 39). For the fortunate 15–20% of patients with radiographically-localized disease amenable to resection, the median survival ranges from 17 to 23 months (40). At high-volume institutions with extensive experience, the mortality rate is <3%–5%, but morbidity remains problematic, with early postoperative complication rates of ~30%–40% (6). Perioperative morbidity and mortality rates recorded in national databases, which include data from a broad spectrum of hospitals and surgeons' experiences, report significantly higher numbers of complications than high-volume tertiary referral centers (38). Applying our model of regret theory may indirectly motivate each surgeon to consider their own results with the procedure and to consider the support available within the institution where the procedure is planned when contemplating the best course of action for each patient, further personalizing care.

A significant proportion of patients undergoing resection develop early metastatic disease and have very limited survival, and thus derive no benefit from the operative intervention (i.e., there is no trade-off improvement in quality-of-life). This issue has been addressed with the use of refined definitions of borderline resectability and the use of neoadjuvant therapy (41). Specifically, this minimally effective chemotherapy, which offers virtually no hope of eradicating disease and little if any therapeutic efficacy, does provide a “window of observation”, during which distant metastatic disease may appear and thus spare the patient unnecessary surgery. This approach may minimize regret and results in better overall survival for patients who ultimately undergo resection (42), but it has not been widely adopted across the country or even across academic centers. Similarly, regret theory remains severely underutilized in the healthcare arena, despite considerable conceptual and empiric interest in its applicability, and in the strong influence of regret on physician decision-making (32, 43–45). The lack of incorporation of regret theory into healthcare delivery is particularly perplexing, especially considering that all medical decisions are accompanied by varying degrees of risk and uncertainty, and – therefore – potential regret. Moreover, recent work has suggested that physicians' behavior can often be explained by regret avoidance (46), which further substantiates the need to incorporate regret modeling into healthcare decisions.

As with any novel theoretical work, our application of regret theory to pancreatic adenocarcinoma has limitations. First, we applied the theory retrospectively with assigned cutoff survival values. We assumed maximal regret to be associated with operating on a patient who died within the first seven months following resection. Excluding death as a result of the procedure (perioperative death), which is always associated with regret, death within seven months may not necessarily be associated with regret. For example, a patient may have died of an unrelated stroke that could not have been foreseen prior to resection. Second, our approach has not yet been empirically tested and the prediction model has not been externally validated. Third, the methodology, as presented, is appropriate for point decision-making, and not necessarily for decisions that re-occur over time – as frequently happens in patient care. Finally, we assumed that there is a single decision-maker involved in the process where, in actual practice, a multidisciplinary team of healthcare providers is involved in treatment decisions.

In conclusion, we have described a novel approach to surgical decision-making using the cognitive emotion of regret, which seeks to personalize care. The goal of our work is to power a computerized decision support tool to assist physicians and patients in making better medical decisions. We envision the

tool to be shared by both physician and patient during consultation, in which the physician elicits the patient's preferences towards alternative management strategies.

## ACKNOWLEDGMENTS

This work is partially supported by the Department of Army grant #W81 XWH 09-2-0175. The authors appreciate the assistance of Jane Carver of the University of South Florida Clinical and Translational Science Institute in reviewing this manuscript.

## REFERENCES

1. McPhee JT, Hill JS, Whalen GF, Zayaruzny M, Litwin DE, Sullivan ME, et al. Perioperative mortality for pancreatectomy: a national perspective. *Annals of surgery*. 2007;246(2):246.
2. Vollmer CM, Sanchez N, Gondek S, McAuliffe J, Kent TS, Christein JD, et al. A root-cause analysis of mortality following major pancreatectomy. *Journal of Gastrointestinal Surgery*. 2011;1-15.
3. Baxter NN, Whitson BA, Tuttle TM. Trends in the treatment and outcome of pancreatic cancer in the United States. *Annals of surgical oncology*. 2007;14(4):1320-6.
4. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer statistics, 2008. *CA: a cancer journal for clinicians*. 2008;58(2):71-96.
5. Cress RD, Yin D, Clarke L, Bold R, Holly EA. Survival among patients with adenocarcinoma of the pancreas: a population-based study (United States). *Cancer Causes and Control*. 2006;17(4):403-9.
6. Beger HG, Rau B, Gansauge F, Poch B, Link KH. Treatment of pancreatic cancer: challenge of the facts. *World journal of surgery*. 2003;27(10):1075-84.
7. Pauker SG, Kassirer JP. Therapeutic decision making: a cost-benefit analysis. *The New England journal of medicine*. 1975;293(5):229.
8. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. *The New England journal of medicine*. 1980;302(20):1109.
9. Abramson MA, Pandharipande P, Ruan D, Gold JS, Whang EE. Radical resection for T1b gallbladder cancer: a decision analysis. *HPB*. 2009;11(8):656-63.
10. Aloia TA, Fahy BN. A decision analysis model predicts the optimal treatment pathway for patients with colorectal cancer and resectable synchronous liver metastases. *Clinical Colorectal Cancer*. 2008;7(3):197-201.
11. Kattan MW, Cowen ME, Miles BJ. A decision analysis for treatment of clinically localized prostate cancer. *Journal of general internal medicine*. 1997;12(5):299-305.
12. Kulkarni GS, Finelli A, Fleshner NE, Jewett MAS, Lopushinsky SR, Alibhai SMH. Optimal management of high-risk T1G3 bladder cancer: a decision analysis. *PLoS medicine*. 2007;4(9):e284.
13. Lotan Y, Cadeddu JA, Lee JJ, Roehrborn CG, Lippman SM. Implications of the prostate cancer prevention trial: a decision analysis model of survival outcomes. *Journal of clinical oncology*. 2005;23(9):1911-20.
14. Steyerberg EW, Marshall PB, Jan Keizer H, Habbema JDF. Resection of small, residual retroperitoneal masses after chemotherapy for nonseminomatous testicular cancer. *Cancer*. 2000;85(6):1331-41.
15. Telford JJ, Saltzman JR, Kuntz KM, Syngal S. Impact of preoperative staging and chemoradiation versus postoperative chemoradiation on outcome in patients with rectal cancer: a decision analysis. *Journal of the National Cancer Institute*. 2004;96(3):191-201.
16. Baron J. *Thinking and deciding*: Cambridge University Press; 2000.
17. Bell DE, Raiffa H, Tversky A. *Decision making: Descriptive, normative, and prescriptive interactions*: Cambridge University Press; 1988.
18. Dawes RM, Kagan J. *Rational choice in an uncertain world*: Harcourt Brace Jovanovich New York; 1988.
19. Tsalatsanis A, Barnes LE, Hozo I, Djulbegovic B. Extensions to Regret-based Decision Curve Analysis: An application to hospice referral for terminal patients. *BMC Med Inform Decis Mak*. 2011 Dec 23;11(1):77. PubMed PMID: 22196308. Epub 2011/12/27. Eng.
20. Tsalatsanis A, Hozo I, Vickers A, Djulbegovic B. A regret theory approach to decision curve analysis: a novel method for eliciting decision makers' preferences and decision-making. *BMC Med Inform Decis Mak*. 2010;10:51. PubMed PMID: 20846413. Pubmed Central PMCID: 2954854. Epub 2010/09/18. eng.

21. Djulbegovic B, Hozo I. When Should Potentially False Research Findings Be Considered Acceptable? *PLoS Med*. 2007 02/27;4(2):e26.
22. Djulbegovic B, Hozo I, Schwartz A, McMasters KM. Acceptable regret in medical decision making. *Med Hypotheses*. 1999 Sep;53(3):253-9. PubMed PMID: 10580533. eng.
23. Hozo I, Djulbegovic B. When is diagnostic testing inappropriate or irrational? Acceptable regret approach. *Med Dec Making*. 2008;28(4):540-53.
24. Hozo I, Djulbegovic B. Will insistence on practicing medicine according to expected utility theory lead to an increase in diagnostic testing? *Med Dec Making*. 2009;29:320-2.
25. Bell DE. Regret in Decision Making under Uncertainty. *Operations Research*. 1982;30:961-81.
26. Loomes G, Sugden R. Regret theory: an alternative theory of rational choice. *Economic J*. 1982;92:805-24.
27. Zeelenberg M, Pieters R. A theory of regret regulation 1.1. *J Consumer Psychol*. 2007;17:29-35.
28. Velanovich V, Wollner I. Quality of life and performance status in patients with pancreatic and periampullary tumors. *Int J Clin Oncol*. 2011 Aug;16(4):401-7. PubMed PMID: 21347628. Epub 2011/02/25. eng.
29. Royston P, Sauerbrei W. A new measure of prognostic separation in survival data. *Stat Med*. 2004 Mar 15;23(5):723-48. PubMed PMID: 14981672. Epub 2004/02/26. eng.
30. StatCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP; 2011.
31. Cohen SJ, Dobelbower R, Lipsitz S, Catalano PJ, Sischy B, Smith TJ, et al. A randomized phase III study of radiotherapy alone or with 5-fluorouracil and mitomycin-C in patients with locally advanced adenocarcinoma of the pancreas: Eastern Cooperative Oncology Group study E8282. *International Journal of Radiation Oncology\* Biology\* Physics*. 2005;62(5):1345-50.
32. Djulbegovic B, Hozo I, Lyman GH. Linking evidence-based medicine therapeutic summary measures to clinical decision analysis. *MedGenMed*. 2000;2(1):E6.
33. Hunink MM, Glasziou PP, Siegel JE, Weeks JC, Pliskin JS, Elstein AS, et al. Decision making in health and medicine: integrating evidence and values: Cambridge University Press; 2001.
34. Lichtenstein S, Slovic P. The construction of preference: Cambridge University Press; 2006.
35. Stiggelbout AM, De Haes J. Patient preference for cancer therapy: an overview of measurement approaches. *Journal of Clinical Oncology*. 2001;19(1):220-30.
36. Vickers AJ, Cronin AM, Elkin EB, Gonen M. Extensions to decision curve analysis, a novel method for evaluating diagnostic tests, prediction models and molecular markers. *BMC Medical Informatics and Decision Making*. 2008;8(1):53.
37. Kahneman D. Maps of bounded rationality: Psychology for behavioral economics. *American economic review*. 2003;1449-75.
38. Birkmeyer JD, Finlayson SRG, Tosteson ANA, Sharp SM, Warshaw AL, Fisher ES. Effect of hospital volume on in-hospital mortality with pancreaticoduodenectomy. *Surgery*. 1999;125(3):250-6.
39. Gouma DJ, Van Geenen RCI, van Gulik TM, de Haan RJ, de Wit LT, Busch ORC, et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. *Annals of surgery*. 2000;232(6):786.
40. Rudloff U, Maker AV, Brennan MF, Allen PJ. Randomized clinical trials in pancreatic adenocarcinoma. *Surgical oncology clinics of North America*. 2010;19(1):115.
41. Lal A, Christians K, Evans DB. Management of borderline resectable pancreatic cancer. *Surgical oncology clinics of North America*. 2010;19(2):359.
42. Katz MHG, Pisters PWT, Evans DB, Sun CC, Lee JE, Fleming JB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. *Journal of the American College of Surgeons*. 2008;206(5):833-46.
43. Coricelli G. The potential role of regret in the physician–patient relationship: Insights from neuroeconomics. 2008.
44. Djulbegovic B, Hozo I, Beckstead J, Tsalatsanis A, Pauker SG. Dual processing model of medical decision-making. *BMC Medical Informatics and Decision Making*. 2012;12(1):94.
45. Freemantle N. Are decisions taken by health care professionals rational? A non systematic review of experimental and quasi experimental literature. *Health Policy*. 1996;38(2):71-81.
46. Courvoisier DS, Agoritsas T, Perneger TV, Schmidt RE, Cullati S. Regrets associated with providing healthcare: Qualitative study of experiences of hospital-based physicians and nurses. *PLoS One*. 2011;6(8):e23138.

**Table 1. Patient Demographics and SF-36 Scores. Values are the mean  $\pm$  SEM unless otherwise indicated**

|                                        |                     |
|----------------------------------------|---------------------|
| Male : Female, n (%)                   | 70 : 86 (45% : 55%) |
| Age (yr.),                             | 65.9 $\pm$ 10       |
| Stage: n (%)                           |                     |
| I                                      | 61 (39%)            |
| II                                     | 68 (44%)            |
| III                                    | 25 (16%)            |
| 0                                      | 2 (1%)              |
| SF-36 Scores: <sup>1</sup>             |                     |
| Physical functioning                   | 55.2 $\pm$ 31       |
| Role-physical                          | 35.5 $\pm$ 44       |
| Role-emotional                         | 57.4 $\pm$ 46       |
| Bodily pain                            | 55.5 $\pm$ 30       |
| Pretreatment vitality                  | 41.8 $\pm$ 24       |
| Mental health                          | 70.3 $\pm$ 21       |
| Social functioning                     | 60.8 $\pm$ 31       |
| General health                         | 60.7 $\pm$ 22       |
| Patients undergoing resection, n (%)   | 85 (54%)            |
| Patients receiving chemotherapy, n (%) | 103 (66%)           |
| Survival (mo.)                         | 15.7 $\pm$ 25       |

<sup>1</sup>SF-36 Health Survey, rated from 0 to 100 on a Likert scale, with higher scores indicating better health or physical function (ref).

**Table 2. Hazard ratio estimates of the prediction model**

|                              | <b>Hazard Ratio</b> | <b>P&gt; z </b> | <b>[95% conf. interval]</b> |
|------------------------------|---------------------|-----------------|-----------------------------|
| <b>Stage</b>                 | 1.994865            | 0.001           | 1.326723- 2.999486          |
| <b>Pretreatment vitality</b> | .9849276            | 0.030           | .971512- .9985284           |
| <b>Role-physical</b>         | .9884022            | 0.005           | .9803665- .9965038          |

**Figure 1. Dual Visual Analog Scales.** The DVAS are used for the elicitation of the decision maker's threshold probability. The questions depicted are case-specific.

**Figure 2. Decision model for performing surgery on patients suffering from pancreatic adenocarcinoma.**

$s$  denotes the probability of survival,  $S \pm$  denotes surgery or no surgery,  $D \pm$  denotes death or no death,  $U_i$  are the utilities associated with each outcome and  $Rg$  is the regret associated with each action. For example,  $Rg(S-, D+)$  is the regret associated with not performing a surgery for a patient who died within 7 months.

**Figure 3. Overall survival of patients with pancreatic adenocarcinoma expressed as Kaplan-Meier survival and 95% confidence interval bands.** Vertical bars (|) denote censored observations.

**Figure 4. Regret DCA for the survival model constructed using Cox regression on three variables.**

Dashed and dotted line denotes the decision to perform surgery; solid line denotes the decision not to perform surgery on any patient; dashed line denotes the use of the survival model to perform surgery. The optimal strategy is the action that results in the least amount of regret in case it is proven wrong. For threshold probabilities of 0-5%, the optimal strategy is to perform surgery on all patients, while for threshold probabilities greater than 5% the optimal strategy is to consult the survival model. For threshold probabilities between 80-87%, the regret curve associated with the prediction model is subject to noise associated to the error of the prediction model therefore, we assume that the prediction model remains the least regretful strategy.

**Figure 5. Schematic Representation of Decision Model.**

# Identifying homogenous subgroups for individual patient meta-analysis based on Rough

Eleazar Gil-Herrera, Athanasios Tsalatsanis\*, Ambuj Kumar, Rahul Mhaskar, Branko Miladinovic, Ali Yalcin, and Benjamin Djulbegovic

## set theory

**Abstract**— Failure to detect and manage heterogeneity between clinical trials included in meta-analysis may lead to misinterpretation of summary effect estimates. This may ultimately compromise the validity of the results of the meta-analysis. Typically, when heterogeneity between trials is detected, researchers use sensitivity or subgroup analysis to manage it. However, both methods fail to explain why heterogeneity existed in the first place. Here we propose a novel methodology that relies on Rough Set Theory (RST) to detect, explain, and manage the sources of heterogeneity applicable to meta-analysis performed on individual patient data (IPD). The method exploits the RST relations of discernibility and indiscernibility to create homogeneous groups of patients. We applied our methodology on a dataset of 1,111 patients enrolled in 9 randomized controlled trials studying the effect of two transplantation procedures in the management of hematologic malignancies. Our method was able to create three subgroups of patients with remarkably low statistical heterogeneity values (16.8%, 0% and 0% respectively). The proposed methodology has the potential to automatize and standardize the process of detecting and managing heterogeneity in IPD meta-analysis. Future work involves investigating the applications of the proposed methodology in analyzing treatment effects in patients belonging to different risk groups, which will ultimately assist in personalized healthcare decision making.

## I. INTRODUCTION

In medical research, meta-analysis is used to obtain pooled estimates of the treatment effects reported in various clinical research studies. The importance of meta-analysis stems from the necessity to combine research findings that if considered separately they would produce insignificant, non-generalizable, and unavailing results, unfit to inform medical practice. By systematically combining findings from similar studies it is possible to achieve the totality of evidence necessary to evaluate the efficacy of an investigated treatment.

The challenge researchers face when performing meta-analysis is how to integrate studies that present differences in the design, characteristics and reported effects. Such differences are formally acknowledged as heterogeneity and they are defined as any kind of variability among studies [1]. Typically, there are three types of heterogeneity found in meta-analyses: 1. *Methodological*, which refers to variability in the study design and risk of bias (e.g. randomization, allocation concealment, blindness etc.) [2, 3], 2. *Clinical*, which refers to the variability in the participants, interventions and outcomes studied (e.g. age, race, disease severity, disease progression, past treatment etc.) [2, 3], and 3. *Statistical*, which refers to variability in the observed outcomes [1, 3]. Failure to detect heterogeneity leads to misinterpretation of the summary effect estimates, which jeopardize the quality of the meta-analyses [2, 3] and may produce faulty estimations of the effects magnitude [4, 5]. Both methodological and clinical heterogeneity may result in statistical heterogeneity [6]. Researchers focus primarily on detecting statistical heterogeneity and subsequently on determining whether such heterogeneity is caused due to methodological or clinical variations between studies [1].

Assessing statistical heterogeneity relies on approaches that involve hypothesis testing [1, 7-9], such as the Chochrane's chi-square (Q) [10] and the  $I^2$  measure [9, 11]. Higher values on these tests indicate high heterogeneity between studies. Both chi-square and  $I^2$  tests focus on detecting heterogeneity yet are unable to identify the specific causes that underlie heterogeneity across studies [12]. The burden of explaining heterogeneity falls on the researcher.

---

This work was supported by the Department of Army under grant # W81 XWH-09-2-0175. The study was approved by the University of South Florida institutional review board (IRB # 100701).

E. Gil-Herrera A. Tsalatsanis, A. Kumar, R. Mhaskar, B. Miladinovic and B. Djulbegovic are with the Division of Evidence Based Medicine, Dept. of Internal Medicine, University of South Florida, Tampa, FL 33612, USA (e-mails: eleazar, atsalats, akumar1, rmhaskar, bmiladin, bdjulbeg @health.usf.edu)

A. Yalcin is with the Department of Industrial and Management System Engineering, University of South Florida, Tampa, FL 33620, USA (e-mail: ayalcin@usf.edu).

To explore and explain the observed heterogeneity, meta-analysts conduct sensitivity analysis, based on the methodological quality of studies, and sub group analysis, based on a pre-specified trial or patient characteristics [3]. That is, the trials included in the meta-analysis are grouped according to pre-specified criteria. In case of individual patient data meta-analysis patients are grouped according to pre-specified clinical characteristics. However, these pre-specified criteria and clinical characteristics are generated in an ad-hoc manner and rely on the skills and medical knowledge of the researcher performing the meta-analysis. Thus, the results of meta-analysis may potentially differ depending on the experience of the meta-analyst.

Subgroup analysis [13] and meta-regression[14] are also applied to individual patient datasets (IPD) containing patient characteristics that may potentially influence the treatment effects. Determining which set of characteristics can be used to obtain homogeneous groups yields in a complex process, where subgroup analysis and meta-regression have been found prone to false positive results and ecological bias.

In this paper, we focus on meta-analyses of individual patient data and we propose a novel methodology to identify homogeneous groups of patients for managing the detected heterogeneity. Our approach is based on Rough Set Theory (RST) [15] and has the potential to automatize the process of creating subgroups of patients with similar characteristics.

The mathematical principles that govern RST rely on the relations between objects. Using RST, we analyze and evaluate all possible relations between patients to obtain the minimum and dispensable information required to generate homogeneous subgroups of patients (i.e. patients with similar characteristics). We envision our methodology to operate in an automatic manner without the researcher intervention in selecting those characteristics that matter in grouping patients for meta-analyses.

## II. Methodology

### A. Dataset

Our dataset consists of individual patient data collected from nine randomized trials studying the effect of Allogeneic Peripheral Blood Stem-cell transplantation (PBSCT) compared to Bone Marrow transplantation (BMT) in the management of hematologic malignancies [16]. In total, 1,111 patients were enrolled. Records of 44 patients containing missing information were removed leaving the dataset with 1067 complete cases. Table 1 describes the details of our dataset.

### B. Rough Set Theory

In RST, a dataset is represented by an information system defined as a pair  $S = (U, A)$  where  $U$  is a non-empty finite set of objects that in our case represents the 1,111 patients. The set  $A$  represents a non-empty finite set of attributes called the condition attributes that corresponds to the characteristics of each patient. For every attribute  $a \in A$ , the function  $U \rightarrow V_a$  makes a correspondence between an object (i.e. a patient) in  $U$  to an attribute value, which is called the value set of  $a$ . For example, from table 1, the value of the attribute

| Variable  | Description                               | Categories                                                                                                                                                                                                                                                                                              | %                                                                                |
|-----------|-------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Age       | Patient age                               | 0: <20<br>1: (20,40]<br>2: (40, 65]                                                                                                                                                                                                                                                                     | 6.25 %<br>47.82%<br>45.93%                                                       |
| Gender    | Patient gender                            | 1: Male<br>2: Female                                                                                                                                                                                                                                                                                    | 59.66%<br>40.34%                                                                 |
| Diag      | Diagnosis category                        | Acute lymphoblastic leukemia (ALL)<br>Acute myelogenous leukemia (AML)<br>Chronic lymphocytic leukemia (CLL)<br>Chronic myelogenous leukemia (CML)<br>Hodgkin's disease (HD)<br>Idiopathic myelofibrosis (IMF)<br>Myelodysplastic syndrome (MDS)<br>Multiple myeloma (MM)<br>Non-hodking lymphoma (NHL) | 12.5%<br>33.52%<br>0.28%<br>43.47%<br>0.09%<br>0.76%<br>5.87%<br>1.04%<br>2.46%  |
| StatTrans | Diagnosis status                          | 0: Favorable (early-stage disease)<br>1: Unfavorable (late-stage disease)                                                                                                                                                                                                                               | 74.62%<br>25.38%                                                                 |
| Mtx       | Methotrexate for GVHD prophylaxis         | 1: Yes<br>0: No                                                                                                                                                                                                                                                                                         | 43.84%<br>56.15%                                                                 |
| CondReg   | Conditioning regimen used                 | 1: Total body irradiation based (TBI)<br>2: Non TBI based                                                                                                                                                                                                                                               | 41.19%<br>58.81%                                                                 |
| GrowthFac | Use of post-transplantation growth factor | 1: G-CSF<br>0: not used                                                                                                                                                                                                                                                                                 | 58.14%<br>41.85%                                                                 |
| Alloc     | Treatment                                 | 1: PBSCT<br>2: BMT                                                                                                                                                                                                                                                                                      | 49.05%<br>50.95%                                                                 |
| Trial     | Origin of the study                       | BR<br>US1<br>No<br>SA<br>FR<br>EBMT<br>CAN<br>US2<br>UK                                                                                                                                                                                                                                                 | 5.30%<br>16.29%<br>5.78%<br>5.10%<br>9.56%<br>30.21%<br>20.36%<br>1.70%<br>3.69% |
| Death     | Overall survival                          | 0: Survive<br>1: Death                                                                                                                                                                                                                                                                                  | 59.75%<br>40.25%                                                                 |

“Age” can be 0, 1 or 2 for a given patient. A dataset including an outcome variable  $d \notin A$ , is termed as a decision system, defined as:  $DS = (U, A \cup \{d\})$ . The decision attribute in our data is the variable “Death” representing the overall survival of a patient given the characteristics described in  $A$ .

### C. Indiscernibility and discernibility relations

Two objects (e.g. patients)  $u, u' \in U$  are indiscernible with respect to a set of condition attributes  $B \subseteq A$  if they have exactly the same values in all attributes, i.e:  $a(u) = a(u') \forall a \in B$ . This relation is called *indiscernibility relation* and is defined as:

$$IND(B) = \{(u, u') \in U^2 : \forall a \in B, a(u) = a(u')\} \quad \forall B \subseteq A \quad (1)$$

The *indiscernibility relation* captures the redundant information in the dataset. Every subset  $B \subseteq A$ , can be used for constructing this relation, however, only subsets that maintain the structure of the original dataset, i.e:  $IND(B) = IND(A)$ , are considered appropriate. Such a subset  $B \subseteq A$ , is termed as an exact reduct. In the case that it would not be possible to obtain an exact reduct, approximated reducts with acceptable quality of approximation are considered. The quality of approximation ( $\alpha_B$ ) of a reduct  $B$  quantifies the proportion of objects correctly allocated in a decision class by using only the attributes in  $B$ , i.e:

$$\alpha_B = \frac{|POS(B)|}{|U|} \quad (2)$$

where,  $POS(B)$  is the set of all objects correctly assigned to the right decision class. In general, the higher the value of  $\alpha_B$ , the more desirable the reduct is for constructing homogeneous subgroups.

On the other hand, the *discernibility relation* accounts for differences between objects in terms of their attribute values, i.e:

$$DIS_{DS}(B) = \{(u, u') \in U^2 : \exists a \in B, a(u) \neq a(u')\} \quad \forall B \subseteq A \quad (3)$$

## III. Identifying homogeneous subgroups in individual patient dataset

We use the indiscernibility relation to build homogenous subgroups based on patients with the same characteristics and we use the discernibility relation to explore the characteristics that differentiate each subgroup. Fig. 1 depicts an overview of the proposed methodology, which is comprised of 4 processes: 1. Obtain reducts; 2. Create homogeneous groups; 3. Regroup based on similarities; and 4. Evaluate groups' heterogeneity.

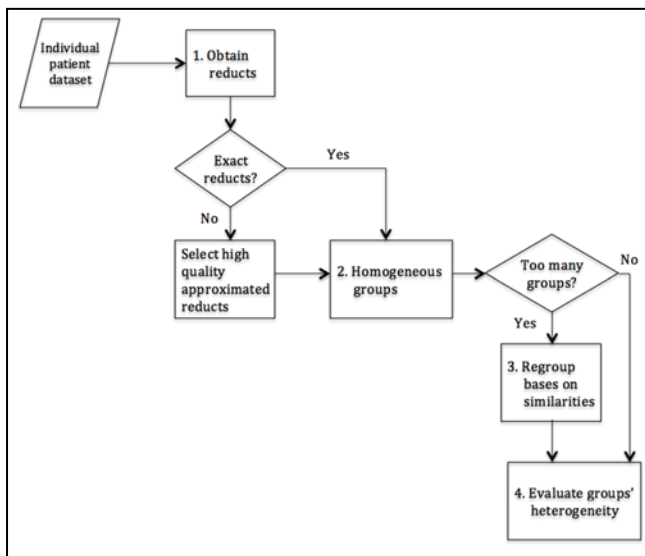


Figure 1. Overview of the RST based methodology for identifying homogeneous subgroups in IPD

**Obtaining reducts:** First, we use the indiscernibility relation  $IND(B)$  to obtain an appropriate subset of condition attributes  $B$  as the basis to generate the homogeneous subgroups of patients. To find this subset of attributes (reducts), we use approximated solutions described in [17]. In our dataset, the set  $B = \{Age, Diag, StatTrans\}$  stands as the approximated reduct with the highest quality of approximation ( $\alpha_B = 0.71$ ) among all the generated reducts.

**Homogeneous groups:** The indiscernibility relation partitions the IPD in 32 disjoint homogeneous subgroups with around 40% of them containing less than 10 patients. Subgroups with small number of patients do not include patients from all trials and are unsuitable for an individual patient meta-analysis.

**Regrouping process:** We obtain subgroups with a larger number of patients by merging smaller subgroups based on a similarity relationship. The similarity relation [18] is defined as a less rigorous version of the indiscernibility relation and is subject to a threshold value that allows small differences considered insignificant. Formally, we define the similarity relation between subgroups as:

$$g_1 \text{ SIM}_{B,\gamma} g_2 \text{ iff } \frac{|X|}{|B|} \geq \gamma, \forall g_1, g_2 \in U/IND(B) \text{ and } u \in g_1 \text{ and } u' \in g_2 \quad (4)$$

Where,  $X = \{a \in B: a(u) = a(u')\}$  and  $\gamma \in [0,1]$  is the similarity threshold.

Since comparing all possible combinations between two groups to determine their similarity is a complex process we use a more straightforward procedure consisting in evaluating the differences between subgroups. Then, subgroups having similar differences to the rest of the subgroups are combined resulting in one homogenous group.

We define a discernibility matrix of subgroups  $\mathcal{M}_B$ , where each cell  $\mathcal{M}_B(g_i, g_j)$  represents the number of attributes in  $B$ , whose values distinguish subgroup  $g_i$  from subgroup  $g_j$ , i.e:

$$\mathcal{M}_B(g_i, g_j) = \{|Dif|\}, \text{ where } Dif = \{a \in B: a(u) \neq a(u')\} \forall g_1, g_2 \in U/IND(B) \text{ and } u \in g_1 \text{ and } u' \in g_2 \quad (5)$$

Fig. 2 shows a portion of the discernibility matrix obtained for the 32 homogenous subgroups.

## IV. results

The initial 32 homogeneous subgroups are regrouped based on similarities in the number of attributes that distinguish them from the rest of groups. We chose a  $\gamma = 0.8$  value (Equation 5) as a threshold parameter of similarity to minimize the number of homogeneous groups by allowing some degree of differences. For example, the initial subgroups 18, 19 and 20 (Fig. 2) can be regrouped since there are no more than 20% of differences across their corresponding rows. In other words, the three subgroups have similar distances, in terms of differences, to the rest of groups. As a result, the 32 homogeneous groups are gathered in three groups. Table 2 shows the homogenous groups resultant after the regrouping process. The mean number of patients in each group is equal to 355 with a standard deviation of 39.15.

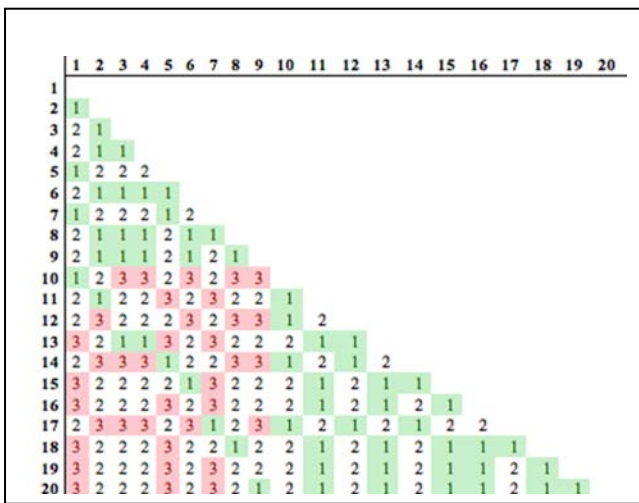


Figure 2. A portion of the discernibility matrix obtained for the homogeneous groups. Each cell shows the number of attributes that differentiate between each pair of subgroups.

| Table 2. Three homogeneous groups obtained from the regrouping process |                                            |                    |
|------------------------------------------------------------------------|--------------------------------------------|--------------------|
| Group number                                                           | Original group                             | Number of patients |
| 1                                                                      | 10, 12, 14, 17                             | 392                |
| 2                                                                      | 21, 23, 26, 29                             | 359                |
| 3                                                                      | 1-9,11,13,15-16,18-20,22,24-25,27-28,30-32 | 314                |

The obtained homogeneous groups (Table 2) contain similar distributions in terms of trials, diagnosis and treatment. The statistical heterogeneity ( $I^2$ ) indicate a negligible heterogeneity value for all the three groups (16.8% in group 1, 0% for group 2, and 0% for group 3), which suggests that all groups are indeed homogeneous.

## V. Conclusions

In this preliminary work, we utilized a methodology typically found in engineering applications to solve a problem that exists in the realm of evidence-based medicine. Researchers who perform evidence synthesis are faced with the challenge of detecting heterogeneity between clinical trials and then explaining it by hypothesizing standards of similarity. However, there is no commonly accepted approach to identify similarities between trials and meta-analysts resolve to ad-hoc solutions. Here we presented a methodology based on Rough Set Theory that has the potential to automatize and standardize this process.

We demonstrated the effectiveness of our methodology using a sample dataset containing 1,111 patients from 9 different trials. We showed that we were able to identify the appropriate patient characteristics to construct homogenous groups that presented similar proportion of trials, controls (diagnosis) and interventions (treatments) in accordance to the fundamental doctrine of meta-analysis. Thus, these groups are suitable to derive the pooled estimate of treatment effects in individual patient meta-analysis.

Other applications of this methodology include identifying subgroups of patients that need different treatments, patients with differential responses to therapy, or patients that belong to different risk groups. Analyzing the effect of treatment in each subgroup is very important for personalized healthcare. Our intention is to compare this methodology with similar approaches in other data sets.

Finally, this is a preliminary work and presents limitations. Particularly, we have not investigated the effects of our methodology in the results of meta-analysis, which we intent to do in the future. Other future research includes generalization of our methodology to accommodate clinical trial data in addition to individual patient data.

## REFERENCES

- [1] J. P. T. Higgins, S. Green, and C. Collaboration, *Cochrane handbook for systematic reviews of interventions* vol. 5: Wiley Online Library, 2008.

- [2] S. L. West, G. Gartlehner, A. J. Mansfield, C. Poole, E. Tant, N. Lenfestey, L. J. Lux, J. Amoozegar, S. C. Morton, and T. C. Carey, "Comparative effectiveness review methods: clinical heterogeneity," 2010.
- [3] J. Higgins and S. Green. (2011). *Cochrane Handbook for Systematic Reviews of Interventions*. Available: <http://www.cochrane.org/resources/handbook/index.htm>
- [4] K. Schulz, "Meta-analyses of interventional trials done in populations with different risks," *Lancet*, vol. 345, p. 1304, 1995.
- [5] E. M. Balk, P. A. L. Bonis, H. Moskowitz, C. H. Schmid, J. P. A. Ioannidis, C. Wang, and J. Lau, "Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials," *JAMA: the journal of the American Medical Association*, vol. 287, pp. 2973-2982, 2002.
- [6] S. G. Thompson, "Why sources of heterogeneity in meta-analysis should be investigated.," *BMJ*, vol. 19, pp. 1351-1355, 1994.
- [7] J. P. Ioannidis, "Interpretation of tests of heterogeneity and bias in meta-analysis," *Journal of Evaluation in Clinical Practice*, vol. 14, pp. 951-957, 2008.
- [8] M. Borenstein, L. V. Hedges, J. P. T. Higgins, and H. R. Rothstein, "Identifying and Quantifying Heterogeneity," in *Introduction to Meta-Analysis*, ed: John Wiley & Sons, Ltd, 2009, pp. 107-125.
- [9] J. Higgins and S. G. Thompson, "Quantifying heterogeneity in a meta-analysis," *Statistics in medicine*, vol. 21, pp. 1539-1558, 2002.
- [10] W. G. Cochran, "Some Methods for Strengthening the Common  $\chi^2$  Tests," *Biometrics*, vol. 10, pp. 417-451, 1954.
- [11] J. Higgins, S. Thompson, J. Deeks, and D. G. Altman, "Measuring inconsistency in meta-analyses," *BMJ*, pp. 327-357, 2003.
- [12] S. G. Thompson and S. J. Sharp, "Explaining heterogeneity in meta-analysis: a comparison of methods," *Statistics in medicine*, vol. 18, pp. 2693-2708, 1999.
- [13] S. W. Wang R Fau - Lagakos, J. H. Lagakos Sw Fau - Ware, D. J. Ware Jh Fau - Hunter, J. M. Hunter Dj Fau - Drazen, and J. M. Drazen, "Statistics in medicine--reporting of subgroup analyses in clinical trials.," *New England Journal of Medicine*, vol. 357, pp. 2189 - 2194, 2007.
- [14] J. Berlin Ja Fau - Santanna, C. H. Santanna J Fau - Schmid, L. A. Schmid Ch Fau - Szczech, H. I. Szczech La Fau - Feldman, and H. I. Feldman, "Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head.," *Statistics in Medicine*, vol. 21, pp. 371-87, 2002
- [15] Z. Pawlak, *Rough Sets: Theoretical Aspects of Reasoning about Data*. Norwell, MA, 1992.
- [16] H. Florida, "Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient data meta-analysis of nine randomized trials," *J Clin Oncol*, vol. 23, pp. 5074-5087, 2005.
- [17] S. Vinterbo and A. Øhm, "Minimal approximate hitting sets and rule templates," *International Journal of Approximate Reasoning*, vol. 25, pp. 123-143, 2000.
- [18] R. Slowinski and D. Vanderpooten, "Similarity relation as a basis for rough approximations," 1995.

## Empirical evaluation of the acceptable regret model of medical decision- making

Athanasios Tsalatsanis<sup>1</sup>, Iztok Hozo<sup>2</sup>, Benjamin Djulbegovic<sup>1</sup>

(1) University of South Florida, Tampa, FL, (2) Indiana University, Gary, IN

**Purpose:** The acceptable regret model postulates that under specific circumstances decision makers may tolerate wrong decisions (*Med Hypotheses*, 53, 253-9; *PLoS Med*, 4, e26; *Med Dec Making*, 28, 540-553; *Med Dec Making*, 29, 320-322). The purpose of this work is to empirically evaluate the acceptable regret model of decision-making in end-of-life care settings, where terminally ill patients consider seeking curative treatment or accepting hospice/palliative care.

**Methods:** We conducted interviews with 24 patients enrolled in the study assessing their preferences about end-of-life treatment choices. After providing information about their life expectancy and assessing the overall regret of potentially wrong choices (*BMC Med Inform Decis Mak*, 10, 51), we elicited the patients' level of acceptable regret. We first assessed the patients' tolerance for wrongly accepting hospice care and then measured the patients' tolerance toward continuing unnecessary treatment. For the purposes of our study, a treatment was considered unnecessary if a patient dies within 6 months of the treatment. Accepting hospice care was considered a wrong decision if a patient survives longer than 6 months after the referral to hospice. We elicited acceptable regret levels to compute: 1) the probability of death above which a patient would tolerate wrongly accepting hospice care and 2) the probability of death below which the patient would tolerate unnecessary treatment (*BMC Med Inform Decis Mak*, 10, 51; *Med Dec Making*, 28, 540-553).

**Results:** We found that the median probability of death above which a decision maker would tolerate wrongly accepting hospice care is 98%, while the median probability of death below which a decision maker would tolerate unnecessary treatment is 4%. We also found that the levels of acceptable regret measured for wrong hospice referral (mean=1.68; SD=2.3; min=0; max=7.28) are similar to the levels of acceptable regret measured for unnecessary treatment (mean=1.27; SD=1.97; min=0; max=6.58) (KW test; p=0.73) indicating that acceptable regret levels for either of wrong decisions is felt similarly. Our results are independent of the estimated probability of death communicated to patients prior to the acceptable regret interview.

**Conclusions:** We have elicited preliminary empirical data that corroborated the acceptable regret theory. Our results may explain why has been so difficult to provide palliative care in the end of life setting.

# BMJ Open From hospice to hospital: short-term follow-up study of hospice patient outcomes in a US acute care hospital surveillance system

Elizabeth Barnett Pathak,<sup>1</sup> Sarah Wieten,<sup>1,2</sup> Benjamin Djulbegovic<sup>1</sup>

To cite: Pathak EB, Wieten S, Djulbegovic B. From hospice to hospital: short-term follow-up study of hospice patient outcomes in a US acute care hospital surveillance system. *BMJ Open* 2014;4:e005196. doi:10.1136/bmjopen-2014-005196

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2014-005196>).

Received 5 March 2014

Revised 1 July 2014

Accepted 4 July 2014

Dr Elizabeth Barnett Pathak;  
[epathak@health.usf.edu](mailto:epathak@health.usf.edu)

## ABSTRACT

**Objectives:** In the USA, there is little systematic evidence about the real-world trajectories of patient medical care after hospice enrolment. The objective of this study was to analyse predictors of the length of stay for hospice patients who were admitted to hospital in a retrospective analysis of the mandatorily reported hospital discharge data.

**Setting:** All acute-care hospitals in Florida during 1 January 2010 to 30 June 2012.

**Participants:** All patients with source of admission coded as 'hospice' (n=2674).

**Primary outcome measures:** The length of stay and discharge status: (1) died in hospital; (2) discharged back to hospice; (3) discharged to another healthcare facility; and (4) discharged home.

**Results:** Patients were elderly (median age=81) with a high burden of disease. Almost half died (46%), while the majority of survivors were discharged to hospice (80% of survivors, 44% of total). A minority went to a healthcare facility (5.6%) or to home (5.2%). Only 9.2% received any procedure. Respiratory services were received by 29.4% and 16.8% were admitted to the intensive care unit. The median length of stay was 1 day for those who died. In an adjusted survival model, discharge to a healthcare facility resulted in a 74% longer hospital stay compared with discharge to hospice (event time ratio (ETR)=1.74, 95% CI 1.54 to 1.97 p<0.0001), with 61% longer hospital stays among patients discharged home (ETR=1.61, 95% CI 1.39 to 1.86 p<0.0001). Total financial charges for all patients exceeded \$25 million; 10% of patients who appeared to exit hospice incurred 32% of the charges.

**Conclusions:** Our results raise significant questions about the ethics and pragmatics of end-of-life medical care, and the intentions and scope of hospices in the USA. Future studies should incorporate prospective linkage of subjective patient-centred data and objective healthcare encounter data.



CrossMark

<sup>1</sup>Division of Evidence-Based Medicine, Morsani College of Medicine, University of South Florida, Tampa, Florida, USA

<sup>2</sup>Department of Philosophy, University of South Florida, Tampa, Florida, USA

Hospice care is a specialised approach to end-of-life medical care that emphasises

- One of the largest studies until now to explore acute-care hospitalisations of hospice patients, a neglected aspect of the dying patient's experience.
- Recent, unbiased and comprehensive surveillance data from the fourth largest state in the USA (Florida) were analysed.
- Detailed analyses of morbidities, in-hospital procedures, length of hospital stay and financial charges were included for four distinct patient groups: patients who died, those who returned to hospice, those who were transferred and those who went home without hospice care.
- Limitations included probable under-reporting of hospice as source of admission; inability to distinguish which morbidity was the terminal illness and lack of information about patient/caregiver preferences for end-of-life care and place of death.

quality of life, pain management and symptom alleviation for terminally ill patients. In the USA, hospice care is usually provided in the patient's home or in a non-hospital facility, and it typically excludes curative-intent medical or surgical interventions. The goal of hospice care is not to prolong life or postpone dying, but rather to achieve a 'good death.' Generally, the preferred length of enrolment in hospice is about 6 months before death, but some guidelines point to a recommended stay of 1 year.<sup>1</sup> As a stipulation for receiving hospice benefits from most US insurance payers, the patient relinquishes access to curative interventions, although the patient can opt out of hospice at any time to regain this access. The idealised patient trajectory that is evoked by hospice advocates is that after patients and families come to terms with the terminal nature of the illness, patients will live out the remainder of their days peacefully at home

## Open Access

or in a hospice facility with minimal medical intervention prior to death.

However, there is very little systematic evidence about the real-world trajectories of patient medical care after hospice enrolment in the USA. Instead, previous hospice studies have focused on whether the use of hospice or advanced directives decrease the cost of end-of-life care<sup>2–4</sup> or increase the quality of life before death.<sup>5 6</sup> These studies of cost and quality of life have generally assumed the idealised trajectory of hospice care, without considering the possible impact of hospitalisations. Previous reports on the phenomenon of post-hospice hospital admissions have been small cohorts<sup>7</sup> or single-centre studies<sup>8 9</sup> and have found that hospitalisation of hospice patients can not only be costly and largely preventable but also that positive patient outcomes for interventions on non-terminal conditions (like hip fractures) might explain some hospice patient hospital admissions.

In this study, one of the largest so far of hospice-to-hospital patients, we analysed very recent data from a statewide hospital surveillance system for all inpatients whose source of admission was coded as ‘hospice.’ We report patient demographics and clinical characteristics; hospitalisation procedures, duration and outcomes; and detailed financial charges. Finally, we modelled predictors of length of hospital stay for the majority of these terminally ill hospice patients who survived to discharge. Given that one of the core goals of hospice programmes in the USA is to avoid unnecessary and futile medical care at the end of life, we presumed that a long hospital stay would constitute a negative and unwanted outcome for most hospice patients.

## METHODS

Our study population consisted of all patients at Florida acute care hospitals whose source of admission was coded ‘hospice’ in the state hospital discharge surveillance system. Other common sources of admission include emergency department, hospital transfer, patient home and skilled nursing facility. In 2010, the reporting requirements were modified and a new code to identify hospice patients was added. In this study, we aggregated 2.5 years of data (1 January 2010 to 30 June 2012) for analysis.

Hospitals in Florida are mandated by state law to submit detailed discharge records of all patients. Consequently, these data can be considered a surveillance system with 100% coverage. Data items available include patient demographics, payer, length of stay, admission diagnosis, principal diagnosis, up to 30 secondary diagnoses, principal and secondary procedure codes and detailed financial charge data.

We analysed data for four distinct groups based on discharge status/destination. The groups were (1) patients who died prior to discharge; (2) patients who were discharged back to hospice (either home hospice care or a hospice facility); (3) patients who were discharged to a

healthcare facility (including transfer to another acute-care hospital, skilled nursing facility, intermediate-care, long-term care or rehabilitation facility); and (4) patients who were discharged home (either with or without home health assistance, but without hospice). For each of our four study groups, we calculated prevalence rates for common admission diagnoses, any-mention diagnoses and procedures. Specifically, ‘any-mention diagnosis’ was based on any mention of a condition in any of 32 diagnosis fields (including admission diagnosis, principal diagnosis and secondary diagnosis fields). Multiple ICD-9-CM codes were combined into categories in some cases. Patients with a diagnosis of heart failure included those with chronic, acute exacerbation or both. A diagnosis of psychosis included those who were suffering from serious behavioural effects of Alzheimer’s disease. While the principal diagnosis code is intended to capture the most serious medical condition suffered by the patient (eg, lung cancer), the admission diagnosis code is intended to identify why the patient was admitted as an inpatient to the hospital (eg, acute respiratory failure). Consequently, admission diagnosis codes may include diseases, symptoms, signs or ‘V-codes’, which are ICD-9-CM codes that describe social circumstances, medical history or other pertinent patient information not captured by traditional organ system-based disease codes. For example, the code V66.7 indicates an episode of palliative healthcare.

Payer categories included Medicare (federal government health insurance for the elderly), Medicaid (federal/state health insurance for low-income persons), Tricare (federal health insurance for military personnel and their dependants), commercial (all non-government health insurance plans including employer-provided plans) and other (including self-pay/underinsured, charity, worker’s compensation and other miscellaneous small programmes).

Procedures (up to 31 per patient) were identified by ICD-9-CM procedure codes. Procedures could include major therapeutic interventions (eg, surgery), minor therapeutic interventions (eg, breathing treatment), diagnostic procedures (eg, MRI, CT scan and colonoscopy) and minor routine procedures (eg, insertion of catheters).

Given that hospital financial coverage is constrained by some payers for hospice patients based on length of stay, we examined predictors of duration of hospital stay using a Weibull accelerated failure (event) time survival model.<sup>10</sup> The Weibull model permits calculation of ‘event time ratios (ETRs)’, which are a more appropriate measure of effect for this study than HRs. This is because our primary interest is not in whether or not an event occurs (all patients eventually leave the hospital), but in whether there are factors that accelerate or delay time to event (ie, days until discharge). ETRs provide a proportional measure of direct impact on time to event (eg, an ETR of 1.25=a 25% increase in the length of hospital stay). We first fit a model with a large number of

potential predictors. For the final model, we retained all covariates with an initial  $p$  value  $\leq 0.15$ .

In addition, some payers will cover occasional hospitalisations of limited duration (eg,  $\leq 5$  days) for hospice patients, for the purposes of respite care or medical attention to a condition which is not the terminal illness.<sup>1–11</sup> Therefore, we used a multivariate logistic regression model to examine the dichotomous outcome of long ( $\geq 6$  days) vs short ( $\leq 5$  days) hospital stays among survivors.

Finally, we examined detailed financial charge data available for each patient as a proxy for costs. We evaluated which charge centres (eg, pharmacy and intensive care) were contributing to total costs both overall and stratified by patient discharge status. We report the percentage of patients with a non-\$0 charge in a given charge centre, and the median and 99th centile dollar values (calculated based only on the distribution of non-\$0 values).

This study was classified as non-human subjects research by the USF Institutional Review Board because it relied solely on de-identified secondary database analyses.

## RESULTS

### Patient discharge status

There were a total of 2764 patients whose source of admission was reported as 'hospice' during the period 1 January 2010 to 30 June 2012 at acute-care general hospitals in Florida. The discharge status of these patients is shown in [figure 1](#). Almost half of these patients died prior to discharge (46%), while the majority of survivors were discharged back into a hospice programme (80% of survivors, 44% of total). Patients discharged home (5.2%) included those who were scheduled to receive home healthcare.

### Patient characteristics, diagnoses and length of stay

Characteristics of patients by discharge status are shown in [table 1](#). The overall median age was 81 years (range 0–106 years); however, non-trivial minorities of each

group were aged  $< 65$  years (12.8–45.7%), and 5% of the patients discharged home were markedly younger than the other three groups (median age=67). The majority of patients were White non-Hispanic (70.8%), followed by Hispanic (19.9%). The majority of patients had Tricare health insurance (51.5%), followed by other (25.4%), private/commercial insurance (16.8%) and Medicare or Medicaid (6.3%).

As expected, these terminally ill patients suffered a high burden of serious illness. The most prevalent diagnoses (based on any mention) are listed in [table 1](#). Some of these conditions were chronic diseases (eg, hypertensive disease, any heart disease, cancer and chronic obstructive pulmonary disease (COPD)), while others probably reflected acute conditions that may have precipitated hospital admission (eg, respiratory failure, acute renal failure, stroke, pneumonia/influenza and sepsis).

The median length of stay for all patients was 2 days, with a range of 0–99 days. While only 10.7% of hospice patients had a stay of 6 or more days, a longer length of stay was much more prevalent among patients discharged to a healthcare facility (32.9%) or home (21.7%). In contrast, patients who died were most likely to have a length of stay of zero days (22.8%), meaning that those patients died on the same day that they were admitted to the hospital.

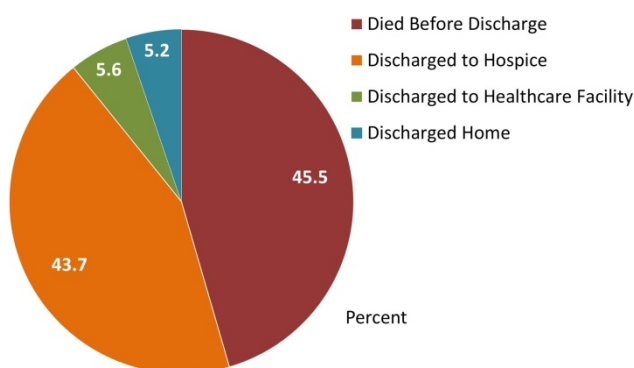
### Admission diagnoses

The top admission diagnoses for patients in our study population are depicted in [figure 2](#). For a terminally ill patient suffering from multiple chronic and acute conditions, the choice of a single admission diagnosis may be somewhat arbitrary. In aggregate, however, these codes provide a window of insight into the diverse challenges present in medical management of the dying patient. Top admission diagnoses among patients who were discharged to a healthcare facility included palliative care (16.1%), cancer (6%), psychosis (4.7%), altered mental status (4%) and pneumonia/influenza (3.4%). Among patients who were discharged home, top diagnoses included cancer (8.7%), respiratory symptoms (7.3%), drug/alcohol dependence (6.5%) and psychosis (6.5%).

### Medical and surgical procedures

Overall, the use of procedures was very limited in this population of terminally ill hospice patients, with only 9.2% overall receiving any procedure ([table 2](#)). Among patients who died, 95.2% received no procedure. Invasive mechanical ventilation was provided in 1% of these patients, and non-invasive mechanical ventilation in 0.8%. At least one procedure was received by 6.8% of patients who were discharged to hospice. In this group, the two most common principal procedures were paracentesis (1%) and transfusion of packed cells (0.9%).

Procedure use was more common among patients who did not return to hospice (33.6% for those who were discharged to a healthcare facility and 41.3% for those who



**Figure 1** Discharge outcomes for patients admitted to a hospital from hospice, Florida 2010–2012 (n=2674).

## Open Access

**Table 1** Characteristics\* of patients admitted from hospice by final discharge status, Florida 2010–2012

|                                       | Died before discharge (n=1217) | Discharged to hospice (n=1170) | Discharged to a healthcare facility (n=149) | Discharged home (n=138) | Total (n=2764) |
|---------------------------------------|--------------------------------|--------------------------------|---------------------------------------------|-------------------------|----------------|
| Median age                            | 80                             | 81                             | 84                                          | 67                      | 81             |
| Age, years (%)                        |                                |                                |                                             |                         |                |
| ≤64                                   | 16.1                           | 15.2                           | 12.8                                        | 45.7                    | 17.1           |
| 65–74                                 | 18.1                           | 14.9                           | 16.1                                        | 18.8                    | 16.6           |
| 75–84                                 | 29.5                           | 30.3                           | 26.2                                        | 21.7                    | 29.2           |
| 85–94                                 | 31.1                           | 33.7                           | 38.3                                        | 9.4                     | 31.5           |
| 95+                                   | 5.3                            | 6.0                            | 6.7                                         | 4.4                     | 5.6            |
| Gender (%)                            |                                |                                |                                             |                         |                |
| Male                                  | 49.1                           | 47.5                           | 38.9                                        | 40.6                    | 47.4           |
| Female                                | 50.9                           | 52.5                           | 61.1                                        | 59.4                    | 52.6           |
| Race/ethnicity (%)                    |                                |                                |                                             |                         |                |
| White                                 | 73.7                           | 69.6                           | 72.5                                        | 52.9                    | 70.8           |
| Hispanic                              | 17.0                           | 22.5                           | 16.8                                        | 26.8                    | 19.9           |
| Black                                 | 6.9                            | 6.7                            | 9.4                                         | 15.2                    | 7.4            |
| Other                                 | 2.4                            | 1.3                            | 1.3                                         | 5.1                     | 2.0            |
| Payer (%)                             |                                |                                |                                             |                         |                |
| Medicare/Medicaid                     | 1.3                            | 4.2                            | 35.6                                        | 37.0                    | 6.3            |
| Private insurance                     | 14.7                           | 19.2                           | 6.0                                         | 26.1                    | 16.8           |
| Tricare/Federal                       | 57.7                           | 49.8                           | 40.3                                        | 23.2                    | 51.5           |
| Other                                 | 26.3                           | 26.8                           | 18.1                                        | 13.8                    | 25.4           |
| 12 Most prevalent diagnoses†          |                                |                                |                                             |                         |                |
| Hypertensive disease                  | 37.6                           | 46.4                           | 62.4                                        | 50.7                    | 43.5           |
| Non-ischaemic heart disease           | 31.1                           | 32.1                           | 38.3                                        | 18.8                    | 31.3           |
| Cancer                                | 28.1                           | 36.6                           | 23.5                                        | 19.6                    | 31.1           |
| Respiratory failure                   | 37.9                           | 18.8                           | 17.5                                        | 10.1                    | 27.0           |
| Ischaemic heart disease               | 25.1                           | 25.0                           | 33.6                                        | 21.0                    | 25.4           |
| Chronic obstructive pulmonary disease | 23.9                           | 25.9                           | 27.5                                        | 21.0                    | 24.8           |
| Heart failure                         | 25.4                           | 22.3                           | 21.5                                        | 19.6                    | 23.5           |
| Psychosis                             | 15.9                           | 28.4                           | 43.6                                        | 28.4                    | 23.5           |
| Acute renal failure                   | 16.7                           | 13.4                           | 18.1                                        | 10.9                    | 15.0           |
| Stroke                                | 15.6                           | 11.8                           | 13.4                                        | 8.7                     | 13.5           |
| Pneumonia or influenza                | 14.1                           | 14.2                           | 12.1                                        | 2.2                     | 13.4           |
| Sepsis                                | 13.6                           | 8.8                            | 9.4                                         | 3.6                     | 10.8           |
| Median length of stay (days)          | 1                              | 2                              | 3                                           | 3                       | 2              |
| Per cent with stay >5 days            | 9.7                            | 7.6                            | 32.9                                        | 21.7                    | 10.7           |

\*All per cents are column per cents.

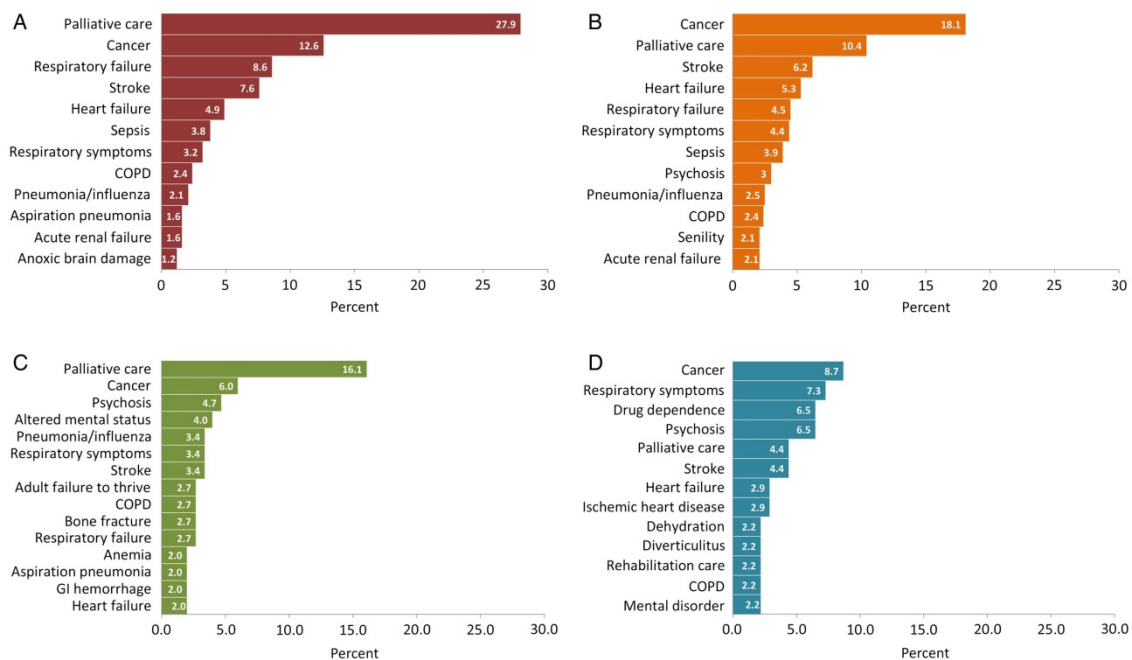
†Based on a mention in any of the 32 diagnosis fields. Each patient could have multiple diagnoses.

were discharged home). Top procedures for hospice patients discharged to a healthcare facility were percutaneous endoscopic gastrostomy (PEG) (3.4%), venous catheterisation (2%) and transfusion of packed cells (2%). For patients discharged home, drug detoxification was the top procedure (5.1%), followed by PEG (2.2%).

### Predictors of the hospital length of stay

We found several significant predictors of length of hospital stay in an accelerated event time survival analysis of all hospice patients who survived to hospital discharge

(n=1457), as shown in [table 3](#). ETRs significantly <1.00 indicate predictors that shortened the length of stay (ie, accelerated time to discharge), while ETRs significantly >1.00 indicate factors that delayed hospital discharge. We first fit a model with a large number of potential predictors. For the final model, we retained all covariates with an initial p value ≤0.15. Potential predictors which were NOT included in the final model were: sex, COPD, ischaemic heart disease, HIV, hypertensive disease, any fracture, respiratory failure, drug/alcohol dependence, sepsis, acute renal failure, end-stage renal disease and



**Figure 2** (A) Top admission diagnoses for hospice patients who died prior to hospital discharge (n=1217). (B) Top admission diagnoses for hospice patients who were discharged back to hospice (n=1170). (C) Top admission diagnoses for hospice patients who were discharged to a healthcare facility (n=149). (D) Top admission diagnoses for hospice patients who were discharged home without hospice care (n=138). COPD, chronic obstructive pulmonary disease; GI, gastrointestinal.

senility. The only patient characteristic that shortened hospital stay was older age. For example, compared with those  $\leq 64$  years of age, patients aged 85–94 years had hospital stays that were 35% shorter (ETR 0.65, 95% CI 0.58 to 0.74,  $p < 0.0001$ ). In contrast, several factors lengthened hospital stays, including Medicare/Medicaid (74% longer stays than those with private insurance), discharge home (61% longer stays than those who

returned to hospice) or to another healthcare facility (74% longer stays than those who returned to hospice) and Hispanic ethnicity (12% longer stays than non-Hispanic Whites). Clinical diagnoses that increased the length of stay included medical complications/infections (43% longer stays than those without these diagnoses), stroke (29% longer stays), heart failure (18% longer stays) and psychosis (13% longer stays). A

**Table 2** Most prevalent principal procedures\* for hospice patients admitted to a hospital, Florida 2010–2012

|                                     | Died before discharge (n=1217) | Discharged to hospice (n=1170) | Discharged to a healthcare facility (n=149) | Discharged home (n=138) | Total (n=2764) |
|-------------------------------------|--------------------------------|--------------------------------|---------------------------------------------|-------------------------|----------------|
| Per cent with no procedure          | 95.2                           | 93.2                           | 66.4                                        | 58.7                    | 91.8           |
| Mechanical ventilation for <96 h    | n=12                           | n=8                            | n=1                                         | n=1                     | n=22           |
| Venous catheterisation              | 6                              | 8                              | 3                                           | 1                       | 18             |
| Blood transfusion                   | 4                              | 11                             | 3                                           | 0                       | 18             |
| Non-invasive ventilation            | 10                             | 5                              | 2                                           | 0                       | 17             |
| Paracentesis                        | 1                              | 12                             | 1                                           | 0                       | 14             |
| Enteral feeding                     | 9                              | 2                              | 0                                           | 0                       | 11             |
| Percutaneous endoscopic gastrostomy | 1                              | 1                              | 5                                           | 3                       | 10             |
| Insertion of an endotracheal tube   | 4                              | 2                              | 2                                           | 0                       | 8              |
| Drug detoxification                 | 0                              | 0                              | 0                                           | 7                       | 7              |
| Haemodialysis                       | 1                              | 3                              | 1                                           | 0                       | 5              |
| Radiation therapy                   | 0                              | 3                              | 1                                           | 1                       | 5              |
| Interruption of vena cava           | 0                              | 2                              | 1                                           | 1                       | 4              |
| Mechanical ventilation $\geq 96$ h  | 1                              | 1                              | 2                                           | 0                       | 4              |

\*All per cents are column per cents. Each patient had one (or no) principal procedure listed.

## Open Access

**Table 3** Predictors of the length of hospital stay among hospice patients who survived to discharge (n=1457): multivariate accelerated event time survival analysis results

| Patient predictors                     | Event time ratio (95% CI) (p value) |
|----------------------------------------|-------------------------------------|
| Discharge destination                  |                                     |
| Hospice                                | 1.00 (referent)                     |
| Healthcare facility                    | 1.74 (1.54 to 1.97) (<0.0001)       |
| Home                                   | 1.61 (1.39 to 1.86) (<0.0001)       |
| Age, years                             |                                     |
| ≤64                                    | 1.00 (referent)                     |
| 65–74                                  | 0.73 (0.64 to 0.84) (<0.0001)       |
| 75–84                                  | 0.69 (0.61 to 0.78) (<0.0001)       |
| 85–94                                  | 0.65 (0.58 to 0.74) (<0.0001)       |
| 95+                                    | 0.72 (0.61 to 0.86) (0.0003)        |
| Race/ethnicity                         |                                     |
| White                                  | 1.00 (referent)                     |
| Hispanic                               | 1.12 (1.03 to 1.22) (0.01)          |
| Black                                  | 1.06 (0.92 to 1.22) (0.44)          |
| Other                                  | 1.82 (1.37 to 2.42) (<0.0001)       |
| Payer                                  |                                     |
| Private insurance                      | 1.00 (referent)                     |
| Medicare/Medicaid                      | 1.74 (1.50 to 2.02) (<0.0001)       |
| Tricare/Federal                        | 1.21 (1.09 to 1.34) (0.0002)        |
| Other                                  | 0.93 (0.84 to 1.04) (0.21)          |
| Clinical diagnoses (present vs absent) |                                     |
| Medical complications/                 | 1.43 (1.18 to 1.73) (0.0002)        |
| infections                             |                                     |
| Stroke                                 | 1.29 (1.15 to 1.44) (<0.0001)       |
| Heart failure                          | 1.18 (1.07 to 1.30) (0.001)         |
| Psychosis                              | 1.13 (1.04 to 1.23) (0.04)          |
| Pneumonia/influenza                    | 1.11 (1.00 to 1.24) (0.06)          |
| Other heart disease*                   | 0.92 (0.85 to 1.01) (0.08)          |
| Cancer                                 | 1.07 (0.98 to 1.17) (0.11)          |

\*Excludes ischaemic heart disease and heart failure. Includes endocarditis, pericarditis, valve disease, cardiomyopathy, pulmonary hypertension and other specified and ill-defined diseases of the heart.

**Table 4** Predictors of a long (≥6 days) vs short (≤5 days) hospital stay among hospice patients who survived to discharge (n=1457): multivariate logistic regression results

| Patient predictors                      | OR (95% CI) (p value)         |
|-----------------------------------------|-------------------------------|
| Age, years                              |                               |
| ≤64                                     | 1.89 (1.08 to 3.33) (0.03)    |
| 65–74                                   | 1.65 (0.96 to 2.85) (0.07)    |
| 75–84                                   | 1.00 (referent)               |
| 85–94                                   | 0.91 (0.55 to 1.49) (0.70)    |
| 95+                                     | 1.16 (0.51 to 2.62) (0.73)    |
| Gender                                  |                               |
| Male                                    | 1.00 (referent)               |
| Female                                  | 1.02 (0.71 to 1.46) (0.94)    |
| Race/ethnicity                          |                               |
| White                                   | 1.00 (referent)               |
| Hispanic                                | 1.13 (0.72 to 1.76) (0.60)    |
| Black                                   | 1.22 (0.65 to 2.28) (0.53)    |
| Other                                   | 1.08 (0.31 to 3.73) (0.91)    |
| Payer                                   |                               |
| Medicare/Medicaid                       | 4.87 (2.50 to 9.51) (<0.0001) |
| Private insurance                       | 1.00 (referent)               |
| Tricare/Federal                         | 2.71 (1.50 to 4.89) (0.001)   |
| Other                                   | 0.86 (0.42 to 1.76) (0.68)    |
| Clinical diagnoses* (present vs absent) |                               |
| Cancer                                  | 1.80 (1.15 to 2.79) (0.01)    |
| Heart failure                           | 1.65 (1.00 to 2.70) (0.047)   |
| Stroke                                  | 1.81 (1.07 to 3.07) (0.027)   |
| Psychosis                               | 1.52 (0.99 to 2.34) (0.059)   |
| Discharge destination                   |                               |
| Hospice                                 | 1.00 (referent)               |
| Healthcare facility                     | 4.67 (2.94 to 7.41) (<0.0001) |
| Home                                    | 2.61 (1.49 to 4.57) (0.0008)  |

\*The following diagnoses were also included in the model and all were insignificant: chronic obstructive pulmonary disease, ischaemic heart disease, pneumonia/influenza, HIV, hypertensive disease, non-ischaemic heart disease, any fracture, complication of medical devices, respiratory failure, drug/alcohol dependence, sepsis, acute renal failure, end-stage renal disease and senility.

diagnosis of cancer did not affect the length of hospital stay (ETR 1.07, p=0.11).

### Predictors of extended hospital stay

Some payers will cover occasional hospitalisations of limited duration (eg, ≤5 days) for hospice patients, for the purposes of respite care or medical attention to a condition which is not the terminal illness.<sup>1 11</sup> Therefore, we used a multivariate logistic regression model to examine the dichotomous outcome of long (≥6 days) vs short (≤5 days) hospital stays among survivors (table 4). We found that patients ≤64 years of age were almost twice as likely to experience a long hospital stay (OR=1.89, 95% CI 1.08 to 3.33, p=0.03) compared with those aged 75–84 years. Gender and race/ethnicity did not predict the length of hospital stay. A total of 18 clinical conditions were included in the model; only 3 conditions were significantly associated with a longer length of stay: cancer (OR=1.80, 95% CI 1.15 to 2.79,

p=0.01), heart failure (OR=1.65, 95% CI 1.00 to 2.70, p=0.047) and stroke (OR=1.81, 95% CI 1.07 to 3.07, p=0.027). Patients with psychosis were 52% more likely to have a long length of stay compared with patients without psychosis, with borderline significance (OR=1.52, 95% CI 0.99 to 2.34, p=0.059).

Finally, consistent with the survival analysis results shown in table 3, the strongest predictors of long versus short stay were payer and discharge destination. Compared with patients insured privately, extended hospital stays were almost five times more likely among those with Medicare or Medicaid (OR=4.87, 95% CI 2.50 to 9.51, p<0.0001), and almost three times more likely among those insured by Tricare (OR=2.71, 95% CI 1.50 to 4.89, p=0.001). Patients who did not return to hospice were several times more likely to have a long hospital stay compared with those who did return to hospice (discharge to the healthcare facility OR=4.67, 95% CI 2.94 to 7.41, p<0.0001; discharge home OR=2.61, 95% CI 1.49 to 4.57, p=0.0008).

### Financial charges

The median hospital charge for patients admitted from hospice was \$3916 (table 5). Reflecting differences in the length of stay, this value varied considerably by discharge status, from \$3424 for patients who died to \$13 293 for patients who were discharged home. The most frequent charge centre was pharmacy, with 91.6% of patients having a non-zero charge, followed by room and board (84.4% of patients), medical/surgical supplies (58.9%), respiratory services and tests (29.4%), intensive care unit (ICU, 16.8%), laboratory (18.7%), radiology/imaging (10.0%) and emergency department (5.6%). Low usage levels for laboratory and radiology are consistent with the intent of exclusion of curative-intent treatment for hospice patients. Patients who did not return to hospice were much more likely to have laboratory charges (57.7–71.0%) and radiology/imaging charges (40.3–44.2%). ICU usage and charges were highest among patients discharged to a healthcare facility and lowest among patients who died.

In summary, total charges for hospice patients admitted to hospitals in Florida during our 30-month study period exceeded \$25 million (table 4). Hospice patients who appeared to be exiting hospice care were 10% (287/2674) of patients by number but incurred 32% (\$8 021 013/\$25 265 839) of the financial charges due to longer lengths of stay, a greater number of procedures and a greater likelihood of ICU use.

### DISCUSSION

This is one of the largest studies to date of a neglected aspect of the experience of dying patients who chose to enrol in hospice. We capitalised on a new data item added in 2010 to Florida's mandatory hospital discharge reporting system which identified patients who were admitted to the hospital from a hospice programme (either home or facility-based). Our study revealed that 46% of patients admitted to the hospital from hospice died before discharge and incurred over \$8 million in charges. Most of these patients died on the day of admission or within 1–2 days after admission and did not receive life-saving procedures, although 18% were admitted to the ICU. This suggests that these hospital admissions were medically unnecessary, which is important given that hospitals are not the preferred place of death for many patients. Research carried out on patients' preferences regarding place of death has shown that in an idealised trajectory of hospice care patients want to die at home or in a hospice facility with minimal medical intervention prior to death.<sup>12</sup> However, for some patients and caregivers, hospital admission in the final hours or days of life may be preferred. For future hospice research, an important patient-centred 'outcome' measure may be whether death occurred in the place and context desired by the patient and family.

A second group of patients admitted to the hospital from hospice care returned to hospice after their stay in the hospital. Many private insurance companies as well

as TriCare and Medicare make allowances for 'respite care' hospital stays of up to 5 days' duration in order to give patients' caregivers a short break. Respite care is consistent with the top two admission diagnoses for this group (cancer and palliative care). However, other admission diagnoses (eg, stroke, respiratory failure/symptoms, sepsis and psychosis) suggest acute illness episodes that home or hospice facility staff were unprepared to cope with. Although there is a substantial body of research on caregiver stress and burnout, this is generally framed as a possible threat to the health of the caregivers themselves rather than a possible reason for hospitalisation from hospice.<sup>13–15</sup> Additional research on a possible link between the preparedness of home and hospice facility staff and acute illness episodes resulting in hospitalisation is warranted.

Importantly, two groups of hospice patients in our study—those discharged to a healthcare facility and those discharged home—were patients whose admission to the hospital most likely denoted a rejection of hospice care. This hypothesis is consistent with our observations that these two groups were more likely to have a stay longer than 5 days, had higher rates of procedure use, and incurred median financial charges that were much higher than those who died or returned to hospice. Although this was a small group of patients, further study on the phenomenon of terminally ill patients exiting hospice treatment is needed.

### Study limitations

Data about the total number of hospice patients in the state of Florida during our study period were not readily available. Hospice care is not subject to regular surveillance, and the large number of relatively small providers of hospice care makes ascertainment of denominator estimates difficult. On the basis of a recent report from a professional organisation,<sup>16</sup> we roughly estimate that there 120 000 hospice patients annually during our study period in Florida. This would translate to about 1% of hospice patients being admitted to hospital. However, while hospital discharge data systems have been shown to be reasonably valid sources of patient information<sup>17–21</sup> and are widely used,<sup>22–25</sup> we believe this new variable to be significantly under-reported, and that the true number of hospice patients admitted was higher. In particular, patients who are admitted via the emergency department (as opposed to a direct admission by the physician) may be less likely to have their hospice status recorded in the medical record.

A second limitation of our study is that these terminally ill patients suffered from multiple chronic and acute diseases and we did not have access to data which identified the initial reason for referral to hospice. An important empirical question is whether the healthcare trajectories of patients dying from cancer, for example, differ in significant ways from those dying from congestive heart failure or COPD.

## Open Access

**Table 5** Detailed financial charges for patients admitted from hospice by final discharge status, Florida 2010–2012

| Charge centres (listed in order of decreasing frequency) | Died before discharge (n=1217) | Discharged to hospice (n=1170) | Discharged to a healthcare facility (n=149) | Discharged home (n=138) | Total (n=2764) |
|----------------------------------------------------------|--------------------------------|--------------------------------|---------------------------------------------|-------------------------|----------------|
| <b>Total</b>                                             |                                |                                |                                             |                         |                |
| Per cent with any charge                                 | 100                            | 100                            | 100                                         | 100                     | 100            |
| Median (\$)                                              | 3424                           | 3634                           | 11 133                                      | 13 293                  | 3916           |
| 99th centile (\$)                                        | 46 755                         | 59 606                         | 310 900                                     | 252 858                 | 100 431        |
| Total for all patients (\$)                              | 8 041 068                      | 9 203 758                      | 4 074 703                                   | 3 946 310               | 25 265 839     |
| <b>Pharmacy</b>                                          |                                |                                |                                             |                         |                |
| Per cent with any charge                                 | 86.9                           | 95.0                           | 98.0                                        | 97.8                    | 91.6           |
| Median (\$)                                              | 434                            | 562                            | 1949                                        | 1427                    | 586            |
| 99th centile (\$)                                        | 25 727                         | 17 099                         | 43 220                                      | 34 186                  | 24 322         |
| <b>Room and board</b>                                    |                                |                                |                                             |                         |                |
| Per cent with any charge                                 | 83.0                           | 86.3                           | 81.9                                        | 82.6                    | 84.4           |
| Median (\$)                                              | 1802                           | 1730                           | 4290                                        | 3912                    | 2106           |
| 99th centile (\$)                                        | 20 400                         | 16 843                         | 31 898                                      | 49 462                  | 22 185         |
| <b>Medical/surgical supplies</b>                         |                                |                                |                                             |                         |                |
| Per cent with any charge                                 | 48.7                           | 67.4                           | 68.5                                        | 66.7                    | 58.9           |
| Median (\$)                                              | 484                            | 484                            | 1,167                                       | 548                     | 525            |
| 99th centile (\$)                                        | 9942                           | 8476                           | 17 892                                      | 193 544                 | 15 048         |
| <b>Respiratory services/tests</b>                        |                                |                                |                                             |                         |                |
| Per cent with any charge                                 | 23.0                           | 33.9                           | 35.6                                        | 40.6                    | 29.4           |
| Median (\$)                                              | 522                            | 585                            | 851                                         | 548                     | 571            |
| 99th centile (\$)                                        | 16 240                         | 7174                           | 78 726                                      | 16 050                  | 16 240         |
| <b>Intensive care unit</b>                               |                                |                                |                                             |                         |                |
| Per cent with any charge                                 | 17.9                           | 14.4                           | 24.8                                        | 19.6                    | 16.8           |
| Median (\$)                                              | 3071                           | 2831                           | 5542                                        | 1915                    | 2990           |
| 99th centile (\$)                                        | 16 276                         | 38 300                         | 62 350                                      | 29 505                  | 32 505         |
| <b>Laboratory</b>                                        |                                |                                |                                             |                         |                |
| Per cent with any charge                                 | 6.9                            | 19.9                           | 57.7                                        | 71.0                    | 18.7           |
| Median (\$)                                              | 506                            | 1041                           | 3337                                        | 1915                    | 1368           |
| 99th centile (\$)                                        | 62 577                         | 37 357                         | 41 047                                      | 35 428                  | 37 357         |
| <b>Radiology/imaging</b>                                 |                                |                                |                                             |                         |                |
| Per cent with any charge                                 | 2.7                            | 9.7                            | 40.3                                        | 44.2                    | 10.0           |
| Median (\$)                                              | 1728                           | 1475                           | 3135                                        | 2310                    | 2018           |
| 99th centile (\$)                                        | 61 895                         | 22 079                         | 61 070                                      | 43 598                  | 48 922         |
| <b>Emergency department</b>                              |                                |                                |                                             |                         |                |
| Per cent with any charge                                 | 1.9                            | 4.6                            | 24.2                                        | 26.1                    | 5.6            |
| Median (\$)                                              | 1999                           | 1886                           | 1647                                        | 1786                    | 1851           |
| 99th centile (\$)                                        | 5089                           | 6134                           | 7189                                        | 5130                    | 6134           |

A final limitation of this study is the lack of information available about patient and family/caregiver decision-making and preferences in relation to hospice care, hospital admission, ICU admission and use of interventions such as mechanical ventilation and blood transfusions. For the patients who died, it is unknown whether dying in the hospital (often shortly after admission) was in accord with patients' and caregivers' wishes, or represented last-minute failures of hospice care to shield patients from unwarranted medical intervention.

### Conclusions and future directions

Our results and those of previous studies<sup>2–9</sup> raise difficult and significant questions about the ethics and pragmatics of end-of-life medical care and the intentions and scope of hospice care. Commonly used templates for patient advance directive documents, for example, 5 Wishes,<sup>26</sup>

include lists of 'life-support treatment' that patients may want to avoid, such as cardiopulmonary resuscitation, mechanical ventilation, tube feeding, major surgery, blood transfusions, dialysis and antibiotics. In our study, the use of procedures was very low, except among patients who survived and did not return to hospice. In a report on hospice patients with hip fracture,<sup>7</sup> 83% received hip surgery and consequently had improved survival compared with those who did not undergo surgery. Patients dying of a terminal disease (eg, cancer) may experience painful and/or life-threatening acute illness events that are completely unrelated in pathology (eg, stroke or hip fracture), and which were not directly addressed in advance directives or hospice care plans. Patients, caregivers and healthcare providers may all find themselves uncertain about the most ethical and compassionate course of action in these situations.

We would advocate inclusion of a simple hospice indicator in additional clinical registries and hospital reporting systems, as this would be a low-cost means of creating additional data resources for exploring hospice patient healthcare trajectories. Future studies should investigate variations in hospice patient healthcare trajectories by cause of terminal illness, as well as incorporate patient and caregiver needs and preferences. An ideal study design would prospectively link subjective patient-centred data (eg, advance directive content, do not resuscitate, patient-reported values and preferences) and objective healthcare encounter data (eg, emergency room visits, inpatient stays and outpatient care).

**Contributors** EBP conceived and designed the study. EBP and SW analysed the data. SW, BD and EBP contributed substantially to interpretation of the data, drafting and revision of the article for important intellectual content and final approval of the version to be published.

**Funding** This study was supported by a USA Department of the Army grant #W81 XWH 09-2-0175 (BD).

**Competing interests** None.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data are available.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

## REFERENCES

- Hospice Facilities Manual. Florida Blue Insurance; August 2012. <http://providermanual.bcbsfl.com/ARS/cr/bg/Pages/Hospice-Facilities.aspx>
- Meng H, Dobbs D, Wang S, et al. Hospice use and public expenditures at the end of life in assisted living residents in a Florida Medicaid waiver program. *J Am Geriatr Soc* 2013;61:1777–81.
- Tan ST, Jatoti A. End-of-life hospital costs in cancer patients: do advance directive or routes of hospital admission make a difference? *Oncology* 2011;80:118–22.
- Weckmann M, Freund K, Bay C, et al. Medical manuscripts impact of hospice enrollment on cost and length of stay of a terminal admission. *Am J Hosp Palliat Care* 2013;30:576–8.
- Teno J, Gozalo P, Casarett D, et al. Does hospice improve quality of care for persons dying from dementia? *J Am Geriatr Soc* 2011;59:1531–6.
- Munn J, Hanson L, Zimmerman S, et al. Is hospice associated with improved end-of-life care in nursing homes and assisted living facilities? *J Am Geriatr Soc* 2006;54:490–5.
- Leland N, Teno J, Gozalo P, et al. Decision making and outcomes of a hospice patient hospitalized with a hip fracture. *J Pain Symptom Manage* 2012;44:458–65.
- Olsen M, Bartlett A, Moynihan T. Characterizing care of hospice patients in the hospital setting. *J Palliat Med* 2011;14:185–9.
- Wallace E, Cooney M, Walsh J, et al. Why do palliative care patients present to the emergency department? Avoidable or unavoidable? *Am J Hosp Palliat Med* 2013;30:253–6.
- Carroll KJ. On the use and utility of the Weibull model in the analysis of survival data. *Control Clin Trials* 2003;24:682–701.
- Medicare Hospice Benefits. Baltimore, MD: Centers for Medicare & Medicaid Services, 2013. <http://www.medicare.gov/Pubs/pdf/02154.pdf>
- Fischer S, Min SJ, Cervantes L, et al. Where do you want to spend your last days of life? Low concordance between preferred and actual site of deal among hospitalized adults. *J Hosp Med* 2013;8:178–83.
- Gitlin L, Rose K. Factors associated with caregiver readiness to use nonpharmacologic strategies to manage dementia-related behavior symptoms. *Int J Geriatr Psychiatry* 2014;29:93–102.
- Otis-Green S, Juarez G. Enhancing the social well-being of family caregivers. *Semin Oncol Nurs* 2012;28:246–55.
- Choi J, Tate K, Sherwood P, et al. Fatigue in family caregivers of adult intensive care unit survivors. *J Pain and Symp Manage* 2014. pii: S0885-3924(13)00666-0. Published Online First: 16 Jan 2014. doi: 10.1016/j.jpainsymman.2013.09.018
- Florida Agency for Health Care Administration. Florida need projections for hospice programs: Background information for use in conjunction with the October 2013 batching cycle for the January 2015 Hospice Planning Horizon. [http://ahca.myflorida.com/MCHQ/CON\\_FA/Publications/docs/FINeedProjections/October2013\\_HospiceNeedProjections.pdf](http://ahca.myflorida.com/MCHQ/CON_FA/Publications/docs/FINeedProjections/October2013_HospiceNeedProjections.pdf). Published 27 Sept 2013 (accessed 27 Jan 2014).
- Quan H, Eastwood C, Cunningham CT, et al.; IMECCHI investigators. Validity of AHRQ patient safety indicators derived from ICD-10 hospital discharge abstract data (chart review study). *BMJ Open* 2013;3:e003716.
- Saczynski JS, Andrade SE, Harrold LR, et al. A systematic review of validated methods for identifying heart failure using administrative data. *Pharmacoepidemiol Drug Saf* 2012;1:129–40.
- Kirkman MA, Mahattanakul W, Gregson BA, et al. The accuracy of hospital discharge coding for hemorrhagic stroke. *Acta Neurol Belg* 2009;109:114–19.
- Quan H, Parsons GA, Ghali WA. Validity of procedure codes in International Classification of Diseases, 9th revision, clinical modification administrative data. *Med Care* 2004;42:801–9.
- De Bruin ML, van Hemel NM, Leufkens HG, et al. Hospital discharge diagnoses of ventricular arrhythmias and cardiac arrest were useful for epidemiologic research. *Clin Epidemiol* 2005;58:1325–9.
- Mark TL, Lawrence W, Coffey RM, et al. The value of linking hospital discharge and mortality data for comparative effectiveness research. *J Comp Eff Res* 2013;2:175–84.
- Lin G, Ma J, Zhang L, et al. Linking cancer registry and hospital discharge data for treatment surveillance. *Health Informatics J* 2013;19:127–36.
- Taylor JA, Pandian RS, Mao L, et al. Using inpatient hospital discharge data to monitor patient safety events. *J Healthc Risk Manag* 2013;32:26–33.
- White RH, Geraghty EM, Brunson A, et al. High variation between hospitals in vena cava filter use for venous thromboembolism. *JAMA Intern Med* 2013;173:506–12.
- Towey J. Aging with Dignity. Five Wishes. 2011. <http://www.agingwithdignity.org/forms/5wishes.pdf>



# From hospice to hospital: short-term follow-up study of hospice patient outcomes in a US acute care hospital surveillance system

Elizabeth Barnett Pathak, Sarah Wieten and Benjamin Djulbegovic

*BMJ Open* 2014 4:

doi: 10.1136/bmjopen-2014-005196

---

Updated information and services can be found at:

<http://bmjopen.bmj.com/content/4/7/e005196.full.html>

---

*These include:*

## References

This article cites 21 articles, 4 of which can be accessed free at:

<http://bmjopen.bmj.com/content/4/7/e005196.full.html#ref-list-1>

## Open Access

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

## Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

---

## Topic Collections

Articles on similar topics can be found in the following collections

[Ethics](#) (33 articles)  
[Geriatric medicine](#) (94 articles)  
[Health services research](#) (491 articles)  
[Palliative care](#) (28 articles)  
[Patient-centred medicine](#) (151 articles)

---

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>