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META-REGRESSION: PROGNOSTIC MODELS AS OBJECTIVE PREDICTORS OF MORTALITY AMONG ICU CANCER PATIENTS

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Dedication

This body of work is dedicated to the beautiful muse in my life, Kennedy N. Donnell.
Thank you for the beauty of inspiration.

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Parents, family members, teachers, peers, friends and strangers are like nutrients sowed into the ground and PhD candidates are the soil. Each nutrient is distinct, serving a unique role to produce healthy soil. The blending of nutrients makes it difficult to decipher the specific meaning of individual encounters and influences. Nevertheless, I am healthy soil due to the nutrient value of important elements in my life. To the nutrients in my life, I say, “thank you.”

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Abstract

META-REGRESSION: PROGNOSTIC MODELS AS OBJECTIVE PREDICTORS OF MORTALITY AMONG ICU CANCER PATIENTS

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Cancer patients admitted to the intensive care unit (ICU) may be experiencing complications of disease or treatment-related effects. While acute complications related to disease and/or its therapeutic management vary in severity, the approach to ICU-centered care is complicated by actual versus perceived risks of poor outcomes. Prognostic models that inform clinical judgment of nurses and physicians may prove helpful in this population. The Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA) are ICU-based models predicting 30-day mortality among the general ICU population. Although studies have been published on use of each model, prognostic accuracy for predicting 30-day, all-cause ICU mortality in the cancer population has yielded mixed results.

The purpose of this study was to determine which prognostic model demonstrated greatest prognostic accuracy among oncology patients. Framed within a derived Prognostic Framework, a meta-analysis of prospective and retrospective cohort studies using literature searches of CINAHL, Cochrane, PubMed and Web of Science databases

spanning 2000 to 2017 timeframe was performed. Meta-regression with a random-effects model was used to summarize area under the receiver-operating characteristic curves (AUCs) to estimate overall predictive accuracy for the APACHE II, SAPS II, and SOFA. After comparing performances, APACHE II demonstrated greatest predictive accuracy.

Keywords: Prognostic models, intensive care unit, cancer, meta-analysis, meta-regression

Chapter 1

Introduction

Critically ill oncology patients admitted to the ICU are a vulnerable at- risk population for clinical bias towards perceived poor prognoses (Bird et al., 2012; Kopterides et al., 2011; Neville et al., 2015). Negative preconceived notions about the clinical response of oncology patients to aggressive medical management in the critical care environment are reflective of biases and misunderstandings related to cancer diagnoses, traditional treatment methods, and past approaches to symptom management (Cruz, Camalionte, & Caruso, 2015; Louie et al., 2013; Mohammed & Peter, 2009). Perception of prognosis is often demarcated between specialists (oncology experts versus critical care professionals) sharing ICU patients rather than full engagement and thorough information exchange across disciplines (Daly et al., 2016). Information and knowledge gaps compromise clinical perceptions, leaving critically ill cancer patients vulnerable to subjective opinions regarding patients' prognoses of cancer patients (Frost, Cook, Heyland, & Fowler, 2011; Mohan, Alexander, Garrigues, Arnold, & Barnato, 2010; Uy, White, Mohan, Arnold, & Barnato, 2013; Visser, Deliens, & Houttekier, 2014).

The current state of cancer treatment and improved short-term survival outcomes in acute care settings are the catalyst for ensuring objective modes of determining prognoses in the oncology population are applied at the bedside. The 21st century ushered in technological and biomedical advancements in oncology that date back to the signing of the National Cancer Act (NCA) of 1971. Through its legislative edicts, major investments in cancer research have led to historic successes in the areas of improved chemotherapies, biotherapeutic developments, imaging technology, and enhanced side effect management (Conway, Carragher, & Timpson, 2014; Gambhir, 2002; Ozols et al., 2007; Tiwari & Roy, 2012; Vogelzang et al., 2012;

Weissleder, 2006; Wingo et al., 2003). Some patients diagnosed with cancer can now expect favorable prognoses amid serious disease and treatment-related complications requiring intensive care management (Schellongowski et al., 2004; Torres et al., 2016).

Investigation into improving the accuracy of prognostic information is warranted to reduce the subjective nature of perceived poor outcomes at the bedside (Hall, 2017). Relying solely on subjective notions to discriminate between favorable and unfavorable prognoses early into the admission process have not proven to be precise among critical care nurses and physicians (Detsky et al., 2017; Hall, 2017). Outcomes from studies examining predictive prognostic accuracy and concordance between critical care nurses and physicians revealed low accuracy rates and discordance between disciplines (Detsky et al., 2017; Neville et al., 2015). Acquisition of models that accurately discriminate prognosis remain promising. When applied appropriately, prognostic models can contribute important analytical information to guide the clinical care of patients (Detsky et al., 2017; Liu et al., 2015; Sawicka, Owczuk, Wujtewicz, & Wujtewicz, 2014).

Several validated prognostic models (vPMs) are readily available for use in the ICU to predict short-term mortality risk (i.e., 30-day ICU stay). Three of the most widely used vPMs in the critical care environment are the Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA) (Vincent & Moreno, 2010). The vPMs may be utilized to provide information for determining acuity of care among critically ill patients, make nurse-patient assignments, and support patient-family decisions about care. To-date, APACHE II, SAPS II, and SOFA perform well when discriminating between likely survivors and non-survivors in general ICU patient populations (Horster et al., 2012; Keegan, & Soares, 2016; Vincent &

Moreno, 2010). A knowledge gap exists about how well vPMs perform in critically ill ICU cancer sub-populations (Sawicka, Owczuk, Wujtewicz, & Wujtewicz, 2014). Exploring the performances of APACHE II, SAPS II, and SOFA among critically ill ICU cancer patients is an opportunity to determine utility of these tools to critical care staff at the bedside.

Purpose Statement

Performances of APACHE II, SAPS II, and SOFA emerged as objective measures for obtaining a prognosis among critically ill ICU patients. Good performance has been established for each vPM in general ICU populations, but overall performances in an ICU sub-population, such as critically ill cancer patients, have not been established. The primary aim of this study was to identify the vPM demonstrating greatest prognostic accuracy in the critically ill adult oncology ICU sub-population. To address the primary aim, meta-analysis was performed to test pooled results gathered from the best available research.

The APACHE II, SAPS II, and SOFA models were selected based on established validity, objectivity, wide use, and broad acceptance in the critical care medicine domain (Vincent & Moreno, 2010). Each model had been studied in several adult general ICU populations and ICU sub-populations resulting in the assumption that study-level data would be available in the literature. For that reason, measuring the overall performances of APACHE II, SAPS II, and SOFA models using a structured, systematic approach to aggregate the findings of published literature was determined to be the best approach to meeting the study purpose.

Prognostic model performance research commonly includes univariate analysis of variables (e.g., covariates) being tested for a relationship to ICU mortality. Covariates are prognostic indices not captured in the model of interest but determined to be independent outcome determinants of 30-day ICU mortality and/or influence the predictive accuracy of vPMs

(Ramsey et al., 2008). Each vPM aggregates several, though slightly different, physiological variables to determine mortality risk. Examples of physiological variables not included in any vPM algorithms but well-established as indicators of cancer-related mortality outcomes include the patient "performance status" score at the time of ICU admission, serum albumin level, and hydration status (Li et al., 2017; Nwosu et al., 2016; Wolf et al., 2016). Therefore, the secondary aim was to describe covariates reported as independent predictors of 30-day ICU mortality.

Background

The topic of vPM application is broad and discussion of significance in the oncology population is multifaceted. When considering the complexity of cancer patients admitted to the ICU, advances in life-sustaining technology, and changing societal expectations for recovery, accurate prognostication in the ICU becomes emotionally charged and challenging for critical care staff (McDermid & Bagshaw, 2009). Despite the heterogeneity of oncology patients admitted to the ICU, biases against aggressively treating critically ill cancer patients, in general, persist in this setting and creates ethical concerns. Conversely, patients and/or families may request aggressive measures even when care is futile. It is within this context that the predictive accuracy of vPMs has a distinct role to play in the relationship between 30-day intensive care mortality and cancer-specific prognosis in the ICU.

Prognostic Models

General validated prognostic models (vPMs) are tools that offer a systemized way of aggregating physiological variables known to be predictors of survival outcomes in the ICU. For the purpose of conducting a meta-analysis, this study was limited to three vPMs: APACHE II, SAPS II, and SOFA. As generic prognostic systems, the information yielded by each vPM is used to establish 30-day ICU mortality risk among critically ill patient groups (Yu et al., 2014).

Mortality risk is quantified using the values of a set of physiological variables routinely observed and measured in the ICU by critical care nursing and physician staff. Each physiological variable used in a given vPM to generate a prognosis, is measured via ICU-based hemodynamic monitoring apparatuses and laboratory specimens (e.g., serum calcium and potassium). These same variables are reported regularly in critical care nursing documentation; thus, simplifying the steps needed to generate a prognosis at the bedside.

Every vPM performs statistical calculations to produce a raw severity-of-illness (SOI) score and corresponding estimated mortality reported in the form of a percentage. Although the bedside nurse collects and documents the information needed in the medical record, either critical care nurses (CCNs) or intensivists enter the data into a vPM calculator for a mortality probability estimate. A physician then interprets the SOI score and percentage by translating these integers into clinical meaningful information. The information gathering and sharing process among the nurse-physician teams makes providing a prognosis to patients/families a collaborative process between CCNs and intensivists.

The calculation (SOI score and percentage of estimated mortality risk) is translated into terms most appropriate for patient/family levels of education and comprehension. As a stipulation, these systems were validated based on measurements obtained within the first 24-hours of admission for their hypothesized predictive accuracy and must be applied in the same manner. As a result, the worst values observed within the first 24 hours are used for baseline assessments of patient 30-day survival chances as well as determining baseline prognoses (i.e., favorable versus unfavorable).

The function of vPM calculations resulting in SOI scores are based on vital sign measurements and laboratory values of selected physiological variables specified per prognostic

system to predict mortality risk. Values of physiological variables (e.g., serum electrolytes, white blood cells, arterial blood gases, Glasgow coma scale) included in each vPM are weighted according to their known relative impact on 30-day ICU mortality (Vincent & Moreno, 2010). Although the physiological variables, along with importance of their corresponding values, reasonably vary from one prognostic scoring system to the next, each model combines their values for analysis using logistic regression techniques and equations (Vincent & Moreno, 2010). Specifically, multiple logistic regression is used in each vPM to provide the probability of 30-day ICU mortality (Vincent & Moreno, 2010). As a result, vPMs are established objective tools capable of stratifying patients into groups in relation to benefit/non-benefit of aggressive care measures when admitted into the ICU (Leung, McArdle, & Wong, 2011).

Cancer Patients in the ICU

Advances in the delivery of care outside of oncology specialization and the use of life-saving strategies in the acute care setting contribute significantly to the increase in short-term survival outcomes in the ICU. The critical care environment is where specialized knowledge and the actions of non-oncology nurse-physician teams make use of advancements in life-saving strategies that greatly impact 30-day mortality for critically ill persons. This setting was of interest in this study because the number of patients with hematological malignancies and solid tumors admitted to this environment has increased (Torres et al., 2016). Past studies report improved survival outcomes in several subsets of this patient population while no differences in survival outcomes among critically ill cancer patients were observed when compared to general critical care patient mixes (Benoit et al., 2003; Torres et al., 2016).

Similar to the general ICU population, patients admitted to the ICU with a cancer diagnosis have situational needs. For example, treatment-related effects due to anti-cancer agents

(e.g., sepsis, renal toxicity, coagulopathy) can be very serious yet reversible when timely, thoughtful management approaches are delivered in intensive care settings (Parakh et al., 2014). Prognosis related to severe insult to health because of treatment is distinctively different from a cancer prognosis; rather, prospects of recovery are associated with the severity of complication(s) from treatment and how adverse events can be managed best in intensive care environments. In addition, certain cancer types are very aggressive at the time of diagnosis and respond well to treatment, but carry a poor prognosis when left untreated. For example, a disease such as acute promyelocytic leukemia is very aggressive and deadly but "curable". However, it requires appropriate drug combinations administered to a patient under close monitoring conditions most conducive to ICU care practices (Rowland et al., 2013; Walker & Held-Warmkessler, 2010).

Some cancer treatments, such as immunotherapy administered for malignant melanoma requires meticulous nurse monitoring due to life threatening side effects (Yu & Si, 2017). The nurse-to-patient ratio and nursing skill levels unique to the ICU environment are supportive of rigorous patient care needs. Therefore, the critical care nursing staff is readily available to identify serious side effects associated with immunotherapy and facilitate timely care. In this situation, the cancer prognosis is poor due to aggressivenessof disease, while the intent of successful treatment is "cure". Because the physiological demand on the patient is great, ability to tolerate therapy is very challenging, and individual response varies; therefore, improved prognosis is not guaranteed with this type of treatment (Lefebvre et al., 2017).

There are case scenarios more clearly indicative of unfavorable prognosis such as cancer patients with disease states that are terminal. Terminal illness and poor prognosis are clearly established when cancer is no longer responding to available treatments and life-sustaining

strategies in the ICU are ineffective. Physiological processes are overwhelmed, health continues to decline, and death is imminent with absolute certainty. In this case, a patient receives a poor prognosis most befitting of a deteriorating condition and continued efforts to sustain life are reasonably futile.

On the other hand, there are patients with a cancer diagnosis admitted post-operatively with complications related to surgery who recover well. In this scenario, both the cancer prognosis and 30-day ICU prognosis can be favorable. Moreover, if a post-op patient with cancer suffers from a life threatening condition unrelated to the malignancy, it is the 30-day ICU prognosis that is unfavorable. The impetus for exploring the different needs of cancer patients in the ICU is to establish that prognoses ought to be tailored around the immediate acute physiological needs and ICU-specific diagnoses of patients, rather than conditioned beliefs about delivering care perceived to be futile. Nevertheless, proficient, high acuity care delivered by nursing and medical staff in the ICU makes it the setting best suited for accessing optimum nursing care so that critically ill cancer patients have the best chances of survival.

Significance

Patient–Family Centered Experience

Patient ICU experience and family presence at the bedside is a demanding psychological event for both (Bolton, 2016; Nikayin et al., 2016). The experience, for patients and family members, takes place within an environment of high-tech monitoring apparatuses, alarms, and procedures. Studies revealed a lack of emotional support, poor communication, and failure to explain prognosis lead to unknowns that create anxiety, psychological distress, and low satisfaction with care for both patients and family members (Beckstrand, Lamoreaux, Luthy, & Macintosh, 2017; Carlson et al., 2015). The significance of identifying a vPM most predictive of

mortality outcomes in the oncology population is its use as a decision aid to offer emotional support, communicate health status, and explain prognosis.

As decision aids, vPMs use physiological variables to assess severity-of-illness to generate SOI scores so that these clinical factors are transformed into an "estimated-risk of mortality" or prognosis. Using hemodynamic parameters and physiological characteristics of the patient introduces objectivity into clinical reasoning and decision-making so that the patient and family have practical information to make decisions. Observations of hemodynamic monitoring and nursing care become contextual for patients and family members when staff explain how prognosis is clinically derived from the information collected. Patient and family observers believe conclusions are more objective when prognoses appear competently integrated into bedside care and communication (Zier et al., 2008).

Sensitivity to staff presence by patients and families is heightened by a sense of vulnerability and awareness of mortality. Mortality becomes deeply reflective for patients and chance of survival is a focal point of patient/family discourse and decision-making (Hutchison et al., 2016). Information sharing regarding prognosis and demonstrations of competence build trust between the nurse, physician and patient-family relationship triad (Carlson et al., 2015; Hutchison et al., 2016). According to Hutchison et al. (2016), establishing trust early is paramount to limiting conflict that can occur during the care planning process between clinicians and patients or their surrogate decision makers when prognoses is not fully understood.

Discordant prognostic estimates from multiple critical care staff cause patients and/or family members to experience doubt, mistrust, and frustration (White, Engelberg, Wenrich, Lo, & Curtis, 2010; White et al., 2016; Ziers et al., 2012). The importance of establishing vPM performance is to have an objective tool for use as a resource to support predicting prognoses

amidst questionable outcomes and uncertainty. A thoughtful approach by the critical care staff is essential to managing expectations, particularly when clinical judgment is antithetical to patient/family beliefs and desires (Ziers et al., 2012).

Moreover, communicating accurate information, such as SOI scores and estimated mortality risk, are important to allaying concerns patients and families have at a time of critical illness; however, it must be framed in understandable terms to be meaningful (Gigerenzer & Edwards, 2003; White et al., 2016). The value of vPMs is best realized when the complexities of a patient condition are translated into relatable terms by critical care staff that address knowledge deficits and promote realistic expectations at the bedside (Gigerenzer & Edwards, 2003).

Prognosis in the Nursing Process

Admission to the ICU is associated with mortality; however, prognosis and related goals of care are often excluded from the discussion (Hall, 2017; Turnbull et al., 2014). Nursing research indicates CCNs have concerns about the need to take an active role in communicating with patients, families, and physicians the significance of prognosis and setting goals of care reflective of pragmatic approaches to its related health outcomes (Milic et al., 2015). Establishing a prognosis early into the care process helps CCNs identify role expectations and navigate patient/family expectations during the nursing care process.

Although the bedside nurse does not formulate a prognosis, understanding its relevance in the care process promotes the delivery of quality care. The nursing process is central to quality patient care and applied holistically at the bedside to ensure patient well-being. In the assessment phase, the CCN assesses patient and family understanding of prognosis and its relation to setting goals of care. Clinical judgment is exercised to recognize knowledge deficits associated with patient prognosis in the diagnosis phase. Determining approaches to patient and family

information needs are then established in the care planning phase of care. Implementation phase involves eliciting physician perspectives on prognosis, orchestrating a family meeting with key stakeholders, and providing emotional support.

Overall, the nursing process requires assessing and developing a care plan addressing patient and family perspectives such as, knowledge deficits, fears, desires, and expectations about treatments and benefits to health. Nurses are advocates ensuring patients and families understand the care process and communication remains an open exchange for asking questions and verbalizing concerns. A prognosis is explained within the context of individual needs, educational level, understanding, and preferences (Parker et al., 2007). Throughout the care process, the bedside nurse supports patients and families wanting aggressive measures employed, despite unfavorable prognoses. The bedside nurse also supports patients with favorable prognoses who decline certain aggressive measures that would reverse untoward health issues. The process is circular whereby the bedside nurse re-assesses the situation, exercises clinical judgment, modifies the plan if needed, acts on cues from patient and family, and revisits goals of care.

Remaining respectful of preferences and values is key to maintaining quality nursing care regardless of diverging or converging decisions in response to prognosis-related information. Regardless of patient and family attitude towards making major health care decisions, appropriate nursing and medical management requires careful assessment of the situation. Turnbull et al. (2015) stated that intensivists are reluctant to discuss outcomes for critically ill patients in the face of prognostic uncertainty and frequently do not ask surrogates about patient values. In response, a component of nursing care is ensuring the environment is conducive to discussions centered on prognosis so that the patient and family experience resolution of

concerns about health-related unknowns. It is through nurse-physician shared understandings of prognosis and clinical value that patient well-being remains at the center of decision quality.

Theoretical Underpinning

The aim of this study was to identify the vPM demonstrating the greatest prognostic accuracy in the critically ill oncology population. The performances of APACHE II, SAPS II, and SOFA were the primary focus. The performance of each vPM begins with measurements of physiological variables routinely recorded in the ICU. For each model, a mathematical computation is performed using physiological measurements to generate a raw score translated into an estimated risk profile. The estimated risk profile is objective information used in conjunction with clinical reasoning to communicate a prognosis to patients and surrogate decision-makers.

To explain vPM performance at the bedside, a derived Prognostic Framework (Figure 1), built on the underpinnings of three theories, guided the study. The borrowing of theoretical principles collectively describe vPM function (principles of physiology and homeostasis), vPM validity (Bayes reasoning) and vPM objectivity (Sociological Theory of Objectivity) to generate a prognosis in this study. Principles of physiology explain how measurable physiological variables serve as predictors of mortality. Biostatistics modeling is the logic applied to probability testing (conditional probabilities) and estimates of mortality when physiological predictors are aggregated using mathematical computations. Probabilities lead to estimates converted into mortality risks to provide objective information about prognosis. All together, each component affects the ability of the model to provide an accurate estimate of ICU mortality and justify bedside application for individual cancer patients. That is, probability testing applied

to human physiological responses to disease can result in objective information such as 30-day ICU mortality risk.

Homeostasis

Each prognostic model uses physiological variables representative of well-functioning homeostatic control in the human body. Homeostatic control or homeostasis is the degree in which the human body maintains equilibrium in its internal environment (Rizzo, 2016). Homeostatic process is the action of physiological mechanisms controlling human bodily functions and monitoring conditions within organ systems. Examples of homeostasis include the regulation of body temperature, acid-base balance, and electrolyte concentrations despite changes in the internal and external environment. Minor fluctuations in normal blood pressure, breathing pattern, and heart rate in response to physiological/psychological stress are signs of well-functioning homeostasis.

Through a series of complex relationships between different human body systems, physiological processes undergo constant adjustments through negative feedback mechanisms to sustain physiological balance (Rizzo, 2016).Therapeutic interventions in the ICU focus on measuring and restoring physiological balance. Issues such as critical illness, severe injury, and/or prolonged physiological stress can decrease the adaptive capacity of homeostatic function. Decreased adaptive function leads to inadequate homeostatic control and weakened compensatory mechanisms resulting in increased risk of death. When homeostatic processes fail and/or therapeutic measures are ineffective, deterioration of health continues and death is inevitable. Accoring to the Progostic Framework, the initial step requires homeostasis data collection and input.

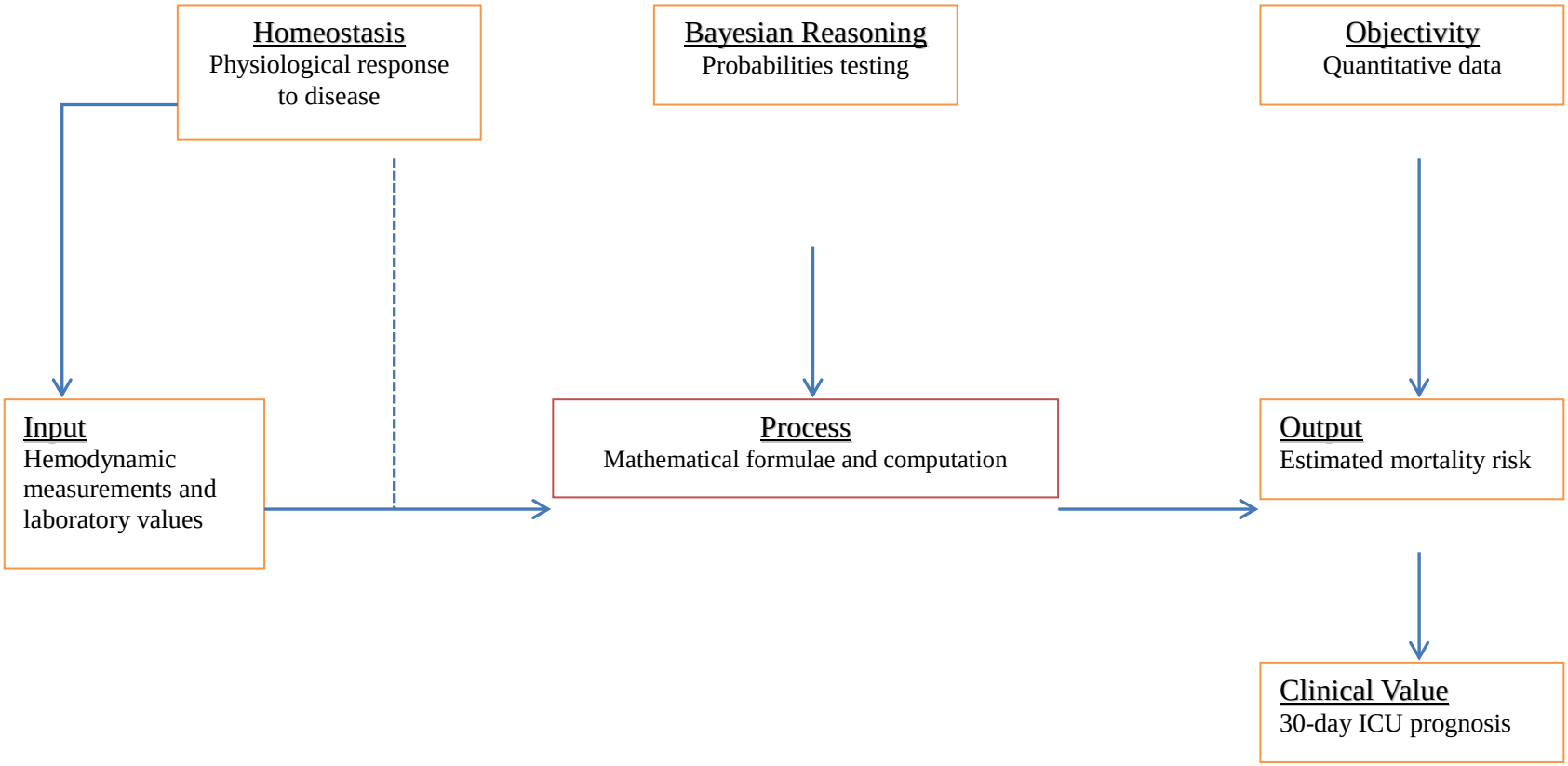

Figure 1. Prognostic Framework

Bayesian Reasoning

Bayes reasoning is the logic that says an external reality (e.g., survival) can be predicted when propositions (i. e., physiological variables) that capture the independent and external reality (states of health) are in place. Bayesian theorem employs a mathematical method based on outcomes from previous studies, prior trials, et cetera to determine the likelihood of that observation occurring in the future (Berger, 2010; Gelman et al., 2013). It involves the use of mathematical calculations to quantify a situation(s) such as critical illness with an uncertain outcome(s) (e.g., 30-day ICU survivor versus non-survivor) as a part of scientific inquiry to reveal an external reality (e.g., 30-day prognosis) (Berger, 2010; Gelman et al., 2013). By objectively quantifying the probability of an event occurring (death), Bayesian reasoning uses probabilistic language and computations to coincide with an independent, external reality (observed mortality). It is a way to show correlation between a predicted reality based on conditional probabilities and observed reality such as 30-day ICU mortality (Barton, Ethier, Duvauferrier, & Burgun, 2017).

The concepts, mathematical language and rules of probability based in Bayesian logic provide the framework for making objective predictions and generating objective prognoses (Barber, 2012; Gelman et al., 2013). The aim is to reach sensible conclusions amid complicated situations like the unpredictable yet complex needs of critically ill cancer patients. Conducting a meta-analysis on this subject matter involved Bayesian indicators of performance: area under the receiver operating characteristic curve (AUC); discrimination and calibration; predictive accuracy; and objectivity (see the "Definition of Terms") (Barbini, Cevenini, Furini, & Barbini 2014; Barton et al., 2017; Marufu et al., 2015).

When reviewing and synthesizing the literature for meta-analysis of prognostic systems, it is important to understand the performance of each vPM within the context of Bayesian indicators of performance. The diagnostic performance statistic used to describe the predictive accuracy of vPM is the AUC. This statistic represents how well a vPM uses propositional logic to assign mortality probabilities to ICU survivors and non-survivors. Predictive performance is assigned a probability measure (AUC values between 0 and 1) based on binary classifications (sensitivity and specificity testing) generated by aggregating conditional variables (physiological parameters) to objectively determine likelihood of an event occurring. In the derived Prognostic Framework, Baysian reasoning guides the creation of an objective indicator based on the homeostatis data from step one.

Objectivity

According to Fuchs Sociological Theory of Objectivity (1997), objectivity is realized when outcomes measuring the same phenomenon independently, correlate strongly with each other and across repeated measurements by several investigators. In this context, performing a meta-analysis is the methodology for making use of a large collection of results gathered from individual studies in order to integrate findings to gain a new objective understanding. It is a way of viewing things dispassionately so that reproducible observations are accepted, applied and communicated as empirical evidence.

Fuchs (1997) argues objectivity requires the scrupulous and pedantic work of stripping away biases and prejudices, as they exist in a profane world. Through a constructivist lens, findings that are inconclusive and/or ambiguous, detract from and hamper objectivity. The nature of objectivity is uncovered through correspondence between accurate statements (or facts) and the external reality. As a product of objective knowledge, a new language evolves out of

reproducible observations; hence, the evidence obtained by means of scientific inquiry disciplines (hold in control) subjectivity of observations in lieu of arbitrary ideas (Fuchs, 1997). In principle, information communicated to the patient-family must be based in the best available evidence rather than influencing factors such as mainstream social ideas, norms, beliefs, relationships, or statuses (Fuchs, 1997).

Objectivity is both empirical and a medium of communication (Fuchs, 1997). Analyzing the findings from a collection of studies is the conduit for establishing evidence-based conversations about vPM function as an objective tool at the bedside and represents the third step in the Prognostic Framework. Through the totality of the evidence, carefully made inferences will inform and guide clinical utility. That is, objectivity sets the rules of scientific inquiry, represents an independent reality and is a hallmark of transferrable impartiality (Fuchs, 1997). As a result, the performances of vPMs act as conduits for *objectivity*, which produce *objective* information for prognosis-related probabilities available to be shared. This process lay at the core of this investigation.

Objectivity in the Nursing Process. Objectivity is an intellectual phenomenon requiring inspecting the methods through which knowledge is formed clinically and subsequently reflected in professional attitudes and behaviors (Engebretsen, Heggen, Wieringa, & Greenhalgh, 2016). Constructing care that is concordant with patient's wishes and values must start by framing prognosis objectively using information inclusive of best and worst-case scenarios to establish balance (Hoerger et al., 2013). Objectivity mediates subjective notions, attitudes, beliefs, and planned actions. By providing a balanced approach using objective prognostic information, professional biases are reduced and patients receive more than one-sided presentations of clinical data (Hoerger et al., 2013).

Re-conceptualizing ICU survival requires that estimates of prognosis are the result of an objective process. Prognosis is a forecast of clinical outcome and its clinical utility is intertwined with patient and family understanding and perspective. Consequently, prognosis makes objectivity an essential component of clinical reasoning, medical decisions, and nursing actions because of risk of harm to the patient (e.g., withholding care when benefit outweighs risk) (Zier et al., 2008; Zier et al., 2012). Nurses and physicians must deliver impartial care and equip patients and family members making treatment decisions with accurate information essential to making value-based decisions regarding treatment (Dugas et al., 2017).

Moreover, nurses use aspects of prognosis to explain evidence-based rationale for care and to be patient advocates while physicians rely on prognosis to justify treatment recommendations. Engebretsen et al. (2016) noted that empirical objectivity is the scientific approach to asking, "Did I observe and/or imagine the situation in the right way?" Objectivity and tools that help clinicians objectively determine probability of mortality is a way of reducing the subjectivity in clinical observations (i.e., predicting short-term prognoses). From this position, objective knowledge is important when subjective views are antithetical to the reality of either favorable or unfavorable short-term outcomes in the ICU.

Research Questions

The primary aim of this study was to answer the question, "Which prognostic scoring system performs 30-day mortality predictions most accurately for critically ill cancer patients admitted to the ICU?" Once identified, the tool with optimal performance can subsequently serve as the model that augments CCN views and advocacy at the bedside as well as inform clinician perceptions, clinical judgment and treatment recommendations. Essentially, the focus was identifying performances of vPMs as a source of objectivity for later use to inform nurse

knowledge and actions as well as physician-based clinical reasoning, which leads to information sharing with patients and families when appropriate.

Overall, the objectivity of the outcome serves as evidence for conversations about the use of vPMs in reducing the subjective nature of both nurse and physician perceptions about patients with a cancer diagnosis in the ICU. Evidence generated from this meta-analysis to answer the research question was a way of identifying a vPM that can be used to build concordance between nurse-physician perspectives at the bedside and application to decision support for patients and families. Because of the availability of three vPMs, the choice of an objective tool offers the impartiality needed when sharing prognosis-related information with patients and families during the shared decision-making process.

The secondary aim was to answer the question, "Among the study sample, what physiological variables are reported to be additional independent predictors of 30-day mortality for oncology patients in the ICU?" By answering this question, clinicians can use the findings to expand clinical knowledge regarding the degree of influence adjunctive physiological variables, not captured in the models, play in SOI scores and estimating risk of 30-day ICU mortality. The answers to both the primary and secondary questions contextualize the use of prognostic scoring systems in critically ill oncology populations. The findings are expected to help CCNs better understand the role of vPM use at the bedside and specific application to the care of oncology patients. For both CCNs and intensivists, the discussion of findings should expand professional knowledge of vPM value to the diversity of ICU patients and how futile care are perceived to healthcare professionals at the bedside.

Definition of Terms

Conducting a meta-analysis centered on the performance outcomes of ICU-based predictive tools and explaining the statistical methodology involves understanding the meaning of Bayesian terminology. Key terms are defined as follows.

Area under the ROC curve (AUC). Area under the curve measures the correlation between the category predicted by the test and the true category into which the case falls and how often predictions and outcomes are concordant (Gonen, 2007; Munro, 2005). The closer the AUC is to 1.0 (e.g., 0.80) the better the performance of prognostic model is at making accurate predictions. For example, an AUC value of 1.0 means the test is perfectly accurate. The practical lower limit for the AUC of a diagnostic test is 0.5 (Gonen, 2007).

Calibration. Calibration is the degree of agreement between a model's predicted probabilities and true (or observed) probabilities using general linear model (GLM).

Cohort. A cohort is a group of subjects sharing a defining characteristic particularly, patients grouped according to the vPM model used to predict mortality.

Discrimination. Discrimination is the degree to which a probability model is able to distinguish between survivors and non-survivors within a 30-day interval (Afessa, Tefferi, Dunn, Litzow, & Peters, 2003; den Boer, de Keizer, & de Jonge, 2005).

Performance. In this study, performance refers to a statistical expression reflecting the degree of concordance between predicted outcome and observed outcome (den Boer, de Keizer, & de Jonge, 2005; Gonen, 2007).

Predictive accuracy. Predictive accuracay is a statistical phrase referring to a calculation of the probability that the test result and prediction agree; the overall precision of a test in measuring true findings. (Munro, 2005).

Summary

Scientific advancements in recent years have resulted in better treatment protocols, greater cure rates and declining mortality rates within the cancer population (NCI, 2015a; NCI, 2015b; Ryerson et al., 2016; Siegel, Miller, & Jemal, 2015). Despite improvements in treatment approaches and supportive care measures, there are instances when patients with active cancer diagnoses require care most befitting in the ICU. The heterogeneity of the critically ill cancer population and varying nature of disease (i.e., curability, reversibility, control, or terminal) makes broad negative assumptions about ICU survival inappropriate. Although the risk of delivering futile care is a legitimate concern in the ICU, the extent of medical intervention cannot be determined by diagnosis of cancer alone. This reality requires ICU survival be re-conceptualized because of diversity in clinical presentations, needs, and available resources to manage critical illness.

Based on research, reluctance among critical care nurses and intensivists to admit critically ill cancer patients to the ICU is attributed to fatalistic views and beliefs about poorer outcomes associated with an active cancer diagnosis (Bird et al., 2012; Kopterides et al., 2011; Neville et al., 2015). In addition, critical care staff have reported experiencing apprehension towards delivering costly care that is perceived as having no benefit to 30-day survival in the ICU (Bos et al., 2015; Cruz, Camalionte, & Caruso, 2015; Kim et al., 2014; Markou, Demopoulou, & Myrianthefs, 2008; Sibbald, Downar, & Hawryluck, 2007). These views persist in spite of improved management strategies available to reverse untoward treatment effects,

control disease, and restore health. Competing factors (set beliefs and perceptions versus patient characteristics and advancements in treatments) cause predicting 30-day ICU mortality to be a conundrum for critical care staff in the absence of an objective medium.

Referencing a prognostic tool is an opportunity to weigh the benefits and risks involved in ICU admission without bias when triaging cancer patients (Cavallazzi et al., 2009). While seeking to provide fair distribution of available ICU resources during triage decisions, clinical inclinations are directed towards ICU patients who are mostly likely to survive if admitted (Blanch et al., 2016). Unfortunately, triaging is taking place under conditions by which decisions for or against ICU admission of cancer patients are often inappropriately focused on the underlying malignant disease rather than the physiological parameters representative of mortality outcomes (Blanch et al., 2016; Cavallazzi et al., 2009; Horster et al., 2012).

Nevertheless, the mathematical probabilities of mortality risk, generated by vPMs, inject objectivity early into the ICU stay (applied within first 24 hours of admission). When applied at admission, the timing of vPM application addresses the subjectivity of traditional beliefs influencing how cancer patients are perceived and concerns about futile care in the early hours of admission to the unit. When used appropriately, vPMs function as objective tools that inform critical care management, critical care nursing action, and support patients and families understanding about the direction of care.

Appropriate use indicates healthcare professionals acknowledge patient-family informational needs. Application also reflects attempts to address anxieties in order to better facilitate the decision-making process in response to both favorable and unfavorable prognoses. The information derived from vPMs does not replace clinical judgment; rather, vPMs add impartial information to clinical reasoning and aid the decision-making process. The intent of

vPM use is to reduce variability in perceptions between nurses at the bedside and intensivists so that patients and family members receive congruent information from staff (Gaeta & Price, 2010). By reviewing and analyzing the literature, additional insights about the performance of vPMs in the cancer population and identification of variables influencing their predictive accuracy broadens the understanding of clinical utility among nursing and medical practice. The intent is translatable findings applicable at the bedside.

Chapter 2

Review of the Literature

Admission to the ICU requires consideration for weighing the benefits of providing advanced life sustaining measures against the risk of excessive measures that do not reverse physiological insult to health. Employing aggressive treatment approaches that do not result in quantifiable or qualitative improvements to patient outcomes (i.e., meaningful survival) is perceived by many critical care staff to be futile care (Cruz, Camalionte, & Caruso, 2015; Louie, et al., 2013; Mohammed & Peter, 2009; von Gruenigen, & Daly, 2005). Moreover, research has shown that ICU clinicians (i.e., intensivists, critical care nurses) continue to reluctantly admit severely ill cancer patients to critical care units because of perceptions of poor prognoses, concern for excessive consumption of resources, and assumptions of delivering costly care that is deemed futile (Bird, Farquhar-Smith, Wigmore, Potter, & Gruber, 2012; Horster et al., 2012; Sibbald, Downar, & Hawryluck, 2007).

Advances in the management of malignancies and complications of treatment resulting in improved survival outcomes make traditional views of cancer patients as poor candidates for admission to the ICU unjustified (Aygencel, Turkoglu, Turkoz-Sucak, & Benekli, 2014; Staudinger et al., 2000). Investigations into ICU mortality among critically ill cancer patients reveal that survival outcomes are comparable with severely ill non-cancer patients (Bird et al., 2012; Ñamendys-Silva et al., 2010; Ñamendys-Silva et al., 2015). Moreover, data demonstrating increase survival rates support the need to incorporate objective modes of determining prognosis into the care planning process.

Distinguishing between medical and surgical causes as well as underlying co-morbidities adds to the complex nature of clinical observation-derived prognoses. Clinical observations in

tandem with negative perceptions and assumptions can distort mortality predictions (Gigerenzer & Edwards, 2003; Zier et al., 2012). When outcomes are poorly conceptualized (i.e., misperceptions of prognosis), patients and families can potentially be harmed by receiving inaccurate information (Gigerenzer & Edwards, 2003; White et al., 2016). In addition, the existence of inter-professional discordance in observations along with biases between critical care nurses and intensivists tend to breakdown collaborative decision-making efforts (Neville et al., 2015; Turnbull et al., 2014). Therefore, objective tools that inform nurse and physician assessments of complex, somber issues inherent to the care of critically ill patients have prognostic implications for guiding care (Neville et al., 2015).

While it is important to recognize that patients with an active cancer diagnosis, including metastatic disease, now have better chances of survival, uncertainty about surviving a 30-day stay in intensive care persists for both patients/families and non-oncology ICU nurses and physicians (Huffines et al., 2013; LeBlanc, Kenny, O'Connor, & Légaré, 2009; Torres et al., 2016). Thoughts of poor prognoses are not unfounded when examining certain patient situations. For example, the uncertainty about a poor prognosis is diminished among patients with well-established terminal illnesses attributed to advancing malignancy and/or irreversible organ failure related to treatment. Through variations and differences in cancer patients needs, clinical presentations serve as the impetus for re-conceptualizing ICU cancer survivors and non-survivors. Prognostic models are the objective approach to mediating clinical judgment when patients are at-risk for biased beliefs about delivering futile care and related outcomes.

Prognosis

Accurate prognosis in the acute care setting is central to clinical decision-making because of its direct relationship to patient outcomes (Mallet et al., 2010). As the endpoint of care,

nursing processes and medical approaches involve patient health status, disease characteristics, and treatment preferences. Together, these factors and related variables determine patient treatment options, inform the direction of care and are influential in predicting short-term survival outcomes (e.g., 30-day ICU survival) (Bird, Farquhar-Smith, Wigmore, Potter, & Gruber, 2012; Bos et al., 2015). Inclusion of prognosis, timeliness of prognostic information, and way of communicating prognosis-related information with patients and/or family decision-makers, serves as the basis for setting realistic expectations in the ICU (Hutchison et al., 2016; LeClaire, Oakes, & Weinert, 2005).

Favorable and unfavorable prognoses in oncology patients are not always apparent at the bedside. Cavallazzi et al. (2009) explained that critically ill patients with malignancies are a heterogeneous group with varied prognoses and specific factors have been associated with different outcomes. Prognostic tools are a way of deciphering between patients most likely to survive and critically ill cancer patients who may not benefit from aggressive treatment approaches (Bos et al., 2015; Moons et al., 2009; Suhag et al., 2014). In this instance, the subjective nature of biases at the bedside are replaced with objective measurements of mortality risk with the use of vPMs. However, discussions about the relationship between prognosis and the role of vPMs in allaying concerns about delivering futile care in the oncology population is absent from the literature.

Prognostic Models

The original development of prognostic models began more than 35 years ago as a means to predict the short-term risk of death (30-day ICU mortality) for ICU patient groups (Vincent & Moreno, 2010). The Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment

(SOFA), are among a few general ICU vPMs available for the adult population (i.e, 18 years and older). These three vPMs are well-established and most frequently used generic prognostic indices reported in the literature (den Boer, de Keizer, & de Jonge, 2005; Tang et al., 2005; Vincent & Moreno, 2010). As popular prognostic tools, APACHE II, SAPS II, and SOFA are readily available online and in the format of "apps" downloaded to personal computers and mobile devices (e.g., Smartphone, tablet computer) at no cost or via subscription to individual users, institutions, and hospital systems. The requirements of use for each vPM are limited to entering the value of the specified physiological variables (e.g., age, hematocrit, temperature) for statistical computation similar to a calculator.

The collection of physiological variables for APACHE, SAPS, and SOFA were selected by way of expert consensus, weighted for mortality prediction through use of statistical modeling techniques, with estimated risk established using multiple logistic regression models (Knaus, Draper, Wagner, & Zimmerman, 1985; LeGall, Lemeshow, & Saulnier, 1993; Vincent et al., 1996). The overall aim was to quantify the natural disease process within the context of therapeutic interventions based on objective criteria. This led to the selection of certain physiological variables routinely measured in the ICU and managed therapeutically in response to clinical aberrations (see Appendix A). These are the combined physiological variables contained in all three vPMs.

Based on the principles of homeostasis, each physiological variable used in a model is an independent predictor of survival outcome. For example, variables representing poor kidney function (creatinine > 4mg/dl), compromised immunity (white blood cells [WBC] < 2.0), and severe respiratory failure (partial pressure of oxygen [PaO2] <80 mm Hg), are signs of homeostatic imbalances driving critical illness and influencing survival outcomes. For clinical

feasibility purposes, particular considerations were given to common variables measured in the ICU that capture homeostatic disequilibrium. Physiological factors like blood pressure, platelets, fraction of inspired oxygen (FiO2), arterial acidity (pH), serum bicarbonate and bilirubin, are accessible in intensive care settings yet objective measurements of physiological health.

Because of the unique characteristics of care in the ICU, conditions of care such as whether or not a patient is receiving mechanical ventilation and use of vasopressors are also included in models' formulae. Specific to model design concerns, focus was directed at simple and practical applications at the bedside for all three vPMs. To promote use, clinical practicability involved interventions that did not go beyond usual activities performed regularly by CCNs and intensivists. For example, the neurological component of the vPMs relies on the Glasgow Coma Scale (GCS) routinely performed by the bedside nurse. This led to reasonable steps to generate mortality risk predictions that are documented with simplicity in the ICU medical record, communicated among healthcare professionals, and shared with patients and families.

The limitation of vPM use entails every field being accurately populated to produce a SOI score and corresponding percentage of estimated mortality risk (e.g., SAPS II total score = 72 points with estimated mortality 86%). Patient needs must align with the physiological parameters of the vPMs for clinical usefulness. Appropriate use requires physicians to order laboratory values, particularly, a basic metabolic panel (BMP), complete blood count (CBC), and bilirubin. In addition, the CCN must receive orders for cardio-respiratory monitoring (including arterial blood gases [ABGs]). Missing data interferes with complete assessment of prognosis; therefore, calculations cannot be performed.

Over time, newer versions of original models (i.e., APACHE to APACHE II and SAPS to SAPS II) have been adapted to accommodate changing patient demographics, disease prevalence, and advancements in intensive care practices. Because of these factors and substantial variations in SOI across different ICU populations, vPMs apply case mix adjustments to statistical formulations and estimates (Livingston et al., 2000). That is, each prognostic model performs statistical procedures to permit comparison of outcomes between providers with differing mix of ICU patients, which allows for validation across multi-unit/site/geographical locations. The development of each vPM takes into consideration broad implications for ICU admission and contributing factors influencing the probability of change in the outcome measure (30-day survivor versus non-survivor) as a means for accommodating heterogeneity in the ICU population (Pappachan, Millar, Bennett, & Smith, 1999).

As stated earlier, vPMs rely on the aggregation of worst values of physiological factors (case mix variables) captured within the first 24 hours of admission. These factors are combined to generate a score that is predictive of ICU-based mortality for each patient. The raw scores are stratified into prognostic indices with higher scores strongly correlating with mortality. Using the rule of general linear model (GLM), the score at time 1 (< 24 hours) is considered the strongest predictor of outcomes due to regression artifacts (Campbell, 1996). Consequently, the raw score (based on worst values) is included in the prediction model for estimating 30-day ICU mortality. Repeated measurements beyond the initial 24-hr monitoring period have not shown to improve vPMs' predictive accuracy (Ferreira et al., 2001; Ho et al., 2007; Minne, Abu-Hanna, & de Jonge, 2008).

The reliability and validation (criterion-related and external validity) of each vPMs' performance (predictive accuracy) are based upon "discrimination" and "calibration" (Keegan &

Soares, 2016). Discrimination refers to a model's ability to make predictions by differentiating between 30-day ICU survivors and 30-day ICU non-survivors with accuracy. It is reported using the area under receiver operating characteristic curve (AUC) which is expressed in the form of a correlation coefficent ranging from 0 to 1 and displayed via a GLM graph.

Discrimination quantifies the accuracy of predictions whereby perfect accuracy is equivalent to an AUC of 1. An AUC closer to 0 is indicative of poor discrimination (e.g., AUC 0.35). For example, a prognostic model predicted 75% mortality within a sample of 100 patients and 75% of the patients died, the AUC will be 1. However, an AUC of .5 indicates the model prediction is equivalent to chance (Keegan & Soares, 2016). It is also another way of describing sensitivity and specificity (i.e., true positive and true negative cases) within the context of prognostic tools. Sensitivity and specificity testing is used to form the receiver operating characteristic curve (ROC) and AUC is the product of sensitivity and specificity results. Table 1 shows the parameters of the scale. The scale ranges from 0 to 1 with 0.5 equivalent to chance. For the scale to be meaningful in the clinical setting, it must perform at 0.7 or better.

Table 1.

Classifying Predictive Accuracy of a Prognostic Test*

Performance Range	*Rating*	*Grade*
.90 – 1	Excellent	A
.80 – .89	Good	B
.70 – .79	Fair	C
.60 – .69	Poor	D
.50 – .59	Fail	F

*Reference ranges retrieved from den Boer, S., de Keizer, N. F., & de Jonge, E. (2005). Performance of prognostic models in critically ill cancer patients - a review. *Critical Care*, 9(4), R458-463. https://dx.doi.org/10.1186/cc3765

As a complement to discrimination, calibration is the degree of agreement between a model's predicted probabilities and true (or observed) probabilities using GLM. It answers the question, "Are the predictions of the model reliable?" (Vergouwe, Steyerberg, Eijkemans, & Habbema, 2002). Calibration is reported statistically using the Hosmer-Lemeshow (H-L) goodness-of-fit test, which gives a chi-square statistic (den Boer, de Keizer, & de Jonge, 2005). When the H-L yields a *p* value greater than 0.05, it is an implication of good calibration while small *p* values (high H-L statistics) indicate lack of fit (Dreiseitl & Osl, 2012; Hosmer, Hosmer, Le Cessie, & Lemeshow, 1997; Vergouwe et al., 2002). When reviewing the literature centered on the performance of prognostic models, authors must report discrimination and calibration to establish validation of vPMs within the respective studies.

External validity is strengthened when study settings include different ICUs, institutions, and/or countries. Mixed populations also expand models' generalizability when good discrimination and validation are achieved under scientific rigor. When reviewing the literature, the aim is to identify validation studies with large samples, diverse populations, multi-sites, and varying geographical locations to establish validation of vPMs that will be used to answer the primary research question. For the aforementioned reasons, APACHE II, SAPS II, and SOFA were presumed to fit the criterion resulting in these models being the focus of the literature review.

APACHE II in the Literature

The Acute Physiology and Chronic Health Evaluation II (APACHE II) is most widely used among prognostic systems around the globe; thus, making it the default gold standard for assessing disease severity on admission to the ICU and formulating outcome predictions (Knaus, 2002; Tang et al., 2005). It currently uses 12 physiological variables and incorporates immuno-

compromised status into its probability prediction (see Appendix B). The score ranges from 0 to 71 with a score of 60 points equaling an estimated mortality of 99.5% as well as a score of 30 and 15 correlating with 75% and 25% risk of mortality, respectively (see Table 2).

Table 2.
Acute Physiology and Chronic Health Evaluation II*

APACHE II Score (points)	Estimated Mortality Risk (%)
0 - 4	4
5 - 9	8
10 - 14	15
15 - 19	25
20 - 24	40
25 - 29	55
30 – 34	75
>34	85

*Publically available at: https://www.mdcalc.com/apache-ii-score

The APACHE prototype was developed in 1981, tested in two ICU settings (a university and community hospital) and validated with 805 patients (Knaus et al., 1981). This original version contained 34 physiologic variables with an increase in score closely correlating with 30-day ICU mortality. The model was then revised 4 years later, in 1985 (APACHE II), to simplify use and increase clinical utility while maintaining the statistical accuracy of the model (Knaus, Draper, Wagner, & Zimmerman, 1985). As a multi-institutional validation study, researchers applied APACHE II in 13 mixed medical-surgical ICUs in the United States. This follow-up study was conducted prospectively between 1979 and 1982 with an enrollment of 5,815 patients (admitted for post-operative, non-operative, emergency, and/or severe chronic conditions monitoring); patients with cancer were included (Knaus, Draper, Wagner, & Zimmerman, 1985). Specifically, all 13 hospitals had a percentage of cancer patients in the study that ranged from 1-11% (Knaus et al., 1985).

Both the developmental and validation studies established APACHE II's clinical validity after it was found to have both good discrimination (> 0.8) and calibration ($p > .05$) as well as generalizable to the ICU population-at-large (Knaus et al., 1981; Knaus et al., 1985). To date, the APACHE II continues to be used and its performance studied worldwide in general and selects ICU patient mixes that include multi-center locations (Livingston et al., 2000, n = 10,393; Nobile et al., 2016, n = 469; Vassar et al., 1999, n = 2,414). As the perceived gold standard among vPMs, researchers have sought its appropriateness for application in high mortality risk groups.

High-risk ICU sub-groups identified in the literature were diverse. Model performance among patients with *cancer* showed good discrimination (Chang et al., 2006, n = 1,263, AUC 0.86, H-L $p = 0.58$). Model performance among patients with cardiac disease was also good (Argyriou et al., 2015, n = 300, AUC 0.84, H-L $p = 0.15$). When APACHE II was applied to trauma patients (Hwang et al., 2012, n = 706, AUC 0.95, H-L $p = 0.3$), those with various infections (Williams et al., 2016, n = 8,871, AUC 0.90, H-L $p = 0.53$), and pulmonary embolism (Chen et al., 2017; n = 55,967, AUC 0.923, H-L p 0.23), it showed excellent discrimination. The ability of APACHE II to discriminate among end stage liver disease patients (Wernly et al., 2017, n = 4,381, AUC 0.76; H-L not reported), cirrhosis (McPhail et al., 2015, n = 971, AUC 0.768, H-L $p = 0.78$), cerebral hemorrhage (Huang et al, 2016, n = 546, AUC 0.76, H-L 0.84); after in-hospital cardiac arrest (Senaratne & Veenith, 2015, n = 261, AUC 0.706, H-L not reported) and individuals over the age of 90 (Haq et al., 2014, n = 951, AUC 0.74, H-L not stated), proved to be less accurate with predicting mortality among the groups studied.

Some validation studies focusing on sub-groups did not include goodness-of-fit tests results. This limited the ability to accept validation solely based on a model's discrimination (reporting AUCs) in those studies. When compared to other generic vPMs (e.g., SAPS II, SOFA)

using both prospective and retrospective study designs, the results have shown good and comparable discriminative ability for predicting outcomes but APACHE II did not always emerge as the superior performing model (Livingston et al., 2000; Nobile et al., 2016; Vassar et al., 1999). Mixed results were identified in APACHE II validation studies centered on cancer patients making it a challenge to establish it as a superior performing prognostic tool in this population (Afessa et al., 2003; Benoit et al., 2003; Berghmans et al.,2004; Schellongowki et al., 2004; Sculier et al., 2000; Soares et al., 2004).

Lastly, the literature review included a search for systematic reviews. Only one of the three systematic reviews identified discussed oncology patients. In this study, APACHE II performance was compared with five other models (including SAPS II but not SOFA) in the critically-ill cancer population (den Boer, de Keizer, & de Jonge, 2005). Among the 10 articles reviewed, only six included APACHE II. The authors surmised that large study design variations made it difficult to perform meaningful comparisons (den Boer et al., 2005). Because of these findings, the optimal performance of APACHE II in the oncology sub-population remained unknown.

SAPS II in the Literature

The Simplified Acute Physiology Score (SAPS) is a validated tool that uses 14 physiological variables for its statistical formulation, which produces a raw score. It also incorporates “age”, “type of admission” (scheduled surgical, unscheduled surgical, or medical), and the presence or absence of three underlying disease variables (acquired immunodeficiency syndrome, metastatic cancer, and hematologic malignancy) into its statistical equation (see Appendix C). The score ranges from 0 to 163 points with a score of 52 points corresponding with 50% mortality, 64 points equaling an estimated mortality of 75% while 77 points yields an

estimated 90% mortality risk (see Table 3). The reliance on continuous variables and categorical variables to devise mortality predictions is the reasoning for GLM statistical approach.

Table 3.
Simplified Acute Physiology Score II*

SAPS II Score (points)	Estimated Mortality Risk (%)
29	10
40	25
52	50
64	75
77	90

*Publically available at: http://clincalc.com/IcuMortality/SAPSII.aspx

It was initially developed in 1984 and applied in eight ICUs with 679 patients participating (Le Gall et al., 1984). It then underwent revision (SAPS II) in 1991and 1992 to refine its probability calculations for converting a raw score into the probability of in-hospital mortality (LeGall, Lemeshow, & Saulnier, 1993). The revised version was developed and applied prospectively. The study analyzed the predictive accuracy of SAPS II among 13,152 patients recruited in 137 medical, surgical, and mixed ICUs from 12 countries (North America and Europe) spanning a 3 month period in 1992 (LeGall et al., 1993).

Each study participant got randomly assigned to the "development" data sample (65%) or "validation" data sample (35%). The study excluded patients under the age of 18, those who were burn victims, and individuals with coronary care needs (including cardiac surgery) from both samples. The patient mix included those with malignancies (solid and hematological) and receiving chemotherapy. In the findings, LeGall, Lemeshow, and Saulnier (1993) reported good discrimination (AUC 0.88) and calibration (H-L $p = 0.883$) for the developmental sample. The validation sample performed similarly with good discrimination (AUC 0.86) and very well with its goodness-of-fit test ($p = 0.104$).

Since its development, additional validation studies have been conducted to evaluate SAPS II performance with other generic vPMs such as comparing it with APACHE II in general ICU case mixes (Godinjak et al., 2016). Godinjak et al. (2016) reported good discrimination, AUC 0.892 and AUC 0.920, for SAPS II and APACHE II respectively in a sample of 174 patients. In addition, Pearson's correlation was used to evaluate the relationship between these two vPMs. The researchers found a positive correlation that was statistically significant between the values of SAPS II and APACHE II ($r = 0.708$; $p = 0.001$).

Lemeshow and LeGall (1994) conducted a systematic review to compare prognostic tools and determine their clinical usefulness. The authors concluded that the evidence supported SAPS II application in assessing prognosis, comparing ICU performance, and stratifying patients for clinical trials. Nevertheless, SAP II model performance in the oncology ICU sub-population was not discussed. This resulted in an identified gap in the literature and interest in further investigation.

International validation studies exploring the predictive performance of SAPS II were also identified in the literature. These studies were conducted inside and outside of the United States. Nobile et al. (2016) investigated its clinical validity in 730 ICUs located in 84 countries but the sample was small ($n = 469$ patients) relative to the study design. Livingston, et al. (2000) performed a large study in Scotland covering 22 ICUs with 13,291 participants but the percentage of cancer patients was not disclosed in the study characteristics or findings. Sakr et al. (2008) study was set in a German university hospital with 1,851 patients. In each of these validation studies, SAPS II demonstrated the best discrimination in comparison with APACHE II but superior calibration over APACHE II was not established. In addition, the investigators did not report the distribution of cancer patients.

More recently, the performance of SAPS II among ICU sub-groups has also been studied to further establish its clinical validity. Outcomes in groups like patients with end stage liver disease (Wernly et al., 2017, n = 4,381, AUC 0.78, H-L not stated), cirrhosis (McPhail et al., 2015, n = 971, AUC 0.781, H-L p = 0.78) and individuals over the age of 90 (Haq et al., 2014, n = 951, AUC 0.75, H-L not stated), showed SAPS II performing fair discrimination and good calibration when reported. This model also showed excellent discrimination and calibration among patients with infectious diseases (Williams et al., 2016, n = 8,871, AUC 0.90, H-L *p* = 0.68). These findings suggest that SAPS II clinical validity and external validation varies among sub-groups in the ICU.

In the cancer ICU sub-population, SAPS II was matched with APACHE II in patients with only hematological malignancies (Benoit et al., 2003) and hematologic/solid tumor case mixes (Schellongowki et al., 2004). Benoit et al. (2003) reported fair discrimination for SAPS II (AUC 0.77) and APACHE II (0.71) with good calibration, 0.60 and 0.39, respectively. Schellongowki et al. (2004) findings showed superior performance for APACHE II (AUC 0.83) over SAPS II (AUC 0.78) with good calibration for both (APACHE II = *p* 0.058; SAPS II = *p* 0.066). On the other hand, Sculier et al. (2000) conducted a comparison study that included patients with metastatic disease that showed poor discrimination (APACHE II AUC 0.60; SAPS II AUC 0.67) and poor calibration (APACHE II *p* 0.001; SAPS II *p* 0.001). Collectively, these results are mixed resulting in the optimal performance of SAPS II in the oncology population yet to be determined.

SOFA in the Literature

The Sequential Organ Failure Assessment (SOFA) is an organ failure based prognostic system and an established predictor of mortality in critically ill patients (Akbar, Shahzadi, Khurram, & Khar, 2016; Vincent et al., 1996). Differing from APACHE II and SAPS II, the SOFA model was created based on the premise that multiple organ failure is a major cause of morbidity and mortality in the critically ill patient and can be assessed repeatedly to define a patient's progress (Vincent et al., 1996; Vincent, Ferreira, & Moreno, 2000). Using physiological variables representative of six organ systems (lungs, bone marrow, brain, heart, kidney, and liver), the SOFA model produces score ranges from 0 to 24 points (see Appendix D). Scores closer to 24 are indicative of greater chance of 30-day ICU mortality (see Table 4).
For example, A score of 12 corresponds with an estimated mortality ranging from 40% to 50% versus a score of 17 points equaling an estimated mortality risk $\geq$ 90%.

Table 4.
Sequential Organ Failure Assessment *

SOFA Score (points)	Estimated Mortality Risk(%)
0 to 6	< 10
7 to 9	15 - 20
10 to 12	40 - 50
13 to 14	50 - 60
15	> 80
15 to 24	> 90

*Publically available at: http://clincalc.com/IcuMortality/SOFA.aspx

The historical development of the SOFA model began in 1994 with a panel of critical care medicine experts. The panel of experts hypothesized that the development of new therapeutic interventions aimed at reducing the severity of organ dysfunction in the ICU called

for better ways to objectively quantify SOI (Vincent et al., 1996). The group posited that the way patients are treated in ICUs as well as therapies used by intensivists to manage organ failure, may change over time. Therefore, a model needed to be constructed with deliberation for how therapeutic advancements and management strategies influence outcomes. This process required a more systematic, objective means for quantifying organ failure to accommodate changing paradigms.

These intentions gave sway to development studies identifying important predictors of mortality (i.e., respiratory-, coagulation-, neurological-, cardiovascular-, renal-, and liver-related variables). Considerations for treatment response and disease progression were parts of the process to successfully establish SOFA's predictive performance (Vincent et al., 1998; Vincent et al, 2000). The actions of model developers subsequently led to validation studies in general ICUs (Toma et al., 2007, n = 6,276, 1 ICU; Toma et al., 2008, n = 2,928, 1 ICU; Ho, 2007, n = 1,311, 1 ICU; Timsit et al., 2002, n = 1,685, 6 ICUs; Rivera-Fernandez et al., 2007, n = 6,409, 55 ICUs) and ICU sub-populations in mixed medical-surgical ICU settings (Ferreira et al., 2001, n = 352; Gosling et al., 2006, n = 431; Moreno et al., 1999, n = 1,449; Zygun et al., 2005, n = 1,436). In addition, the model has been applied across different institutions and geographical locations (Toma et al., 2007, Vincent & Moreno, 2010; Zygun et al., 2005).

There were four validation studies identified that compared admission SOFA predictions with APACHE II's performance in medical and surgical ICU patients. Ho et al. (2007) reported AUCs for SOFA and APACHE II, 0.791 and 0.858, respectively among a population of 1,311 patients. Holtfreter et al. (2006) also conducted a retrospective investigation (n = 933) into the performance of SOFA (AUC 0.72) and found it discriminating more closely to APACHE II (AUC 0.785) but with less accuracy in comparison with the Ho study. Peres-Bota et al. (2002)

approach was a prospective, observational study with 949 patients whereby both models showed good discrimination but APACHE II (AUC 0.88) performed slightly better than SOFA (AUC 0.872). On the other hand, Gosling et al. (2006) employed a prospective approach (n = 431) with both SOFA (AUC 0.61) and APACHE II (AUC 0.62) showing similar, yet poor discrimination.

Janssens et al. (2000) conducted a prospective investigation (n = 303) with SOFA (AUC 0.82) demonstrating superior discrimination in comparison with SAPS II (0.77). Granholm et al. (2016) performed a post hoc study resulting in SOFA (0.73) not discriminating as well as SAPS II (0.80). There was one study identified that compared all three models in a large general hospital in Pakistan. The study enrollment was small with only 96 eligible medical ICU patients (Naqvi et al., 2016). Descriptions of cancer patient makeup were not elucidated in the demographics section. Nevertheless, APACHE II showed somewhat better calibration (*p* 0.866) in comparison to SAPS II (*p* 0.0811) and SOFA (*p* 0.32). With an AUC of 0.835, the APACHE II model showed superior discrimination power to SAPS II and SOFA which both predicted at the same degree of accuracy, AUC = 0.75. Based on these findings, further exploration of SOFA application and optimal performance in the oncology ICU sub-population are warranted, to add to the current body of research.

Bedside Context for Prognostic Models

Because clinical judgment alone is difficult and imprecise, the intent of prognostic model use is to objectively inform clinical judgment; not to replace clinical interpretations or serial assessments (Hamel et al., 1999; Knaus et al., 1995; Teno et al., 2000). Prognostic models are to be regarded as adjunct, objective tools rather than substitutes for clinical judgment and are available for use in the shared decision-making process (Feltracco et al., 2011). The application of prognostic tools within patient-centered clinical pathways and algorithms may assist with

informational needs; thus, ensuring ICU patients receive timely quality care from ICU nurses as well as appropriately prescribed treatments by physicians involved in the care process (Costantini, Alquati, & Di Leo, 2014; Constantini et al., 2014; Huffines et al., 2013).

Again, vPMs aid decisional needs by providing objective information about a patient's clinical status within the first 24 hours of admission to the ICU. These decisional needs are at the center of patient/family directives and guide nurse-physician actions at the initiation of care (Sepucha, Fowler, & Mulley, 2004; Stacey, Samant, & Bennett, 2008; Stacey, Paquet, & Samant, 2010; van Mol, 2016). When the use of prognostic models are understood and applied, nurses use the information for patient advocacy and physicians rely on it to support treatment recommendations (Neville et al., 2015) . The prognostic value is that patients and family as surrogate decision-makers have objective information to address decisional needs that cause uncertainty, reluctance, and desire for additional information (Barbini et al., 2014; Chien et al., 2014; Djulbegovic et al., 2016; Becerra-Perez et al., 2016).

Summary

In summation, APACHE II, SAPS II, and SOFA have been studied in diverse ICU settings (i.e., medical, surgical, neurological, trauma, oncology, cardiac, and surgical units) which included sample sizes greater than 1000 patients on a worldwide platform (Cholongitas et al., 2006; Godinjak et al., 2016; Hosseini & Ramazani, 2016; Naqvi et al., 2016; Pietraszek-Grzywaczewska et al., 2016). Most importantly, APACHE II, SAPS II, and SOFA have been validated using large, prospective, multi-center, multi-national general ICU population mixes (up to 16,000+ patients) that included patients with cancer (Cabré et al., 2005; Livingston et al., 2000; Moreno et al., 1998; Moreno et al., 1999; Salluh & Soares, 2014; Vincent & Moreno, 2010; Yu et al., 2014). The findings support claims that each vPM is good at predicting patient

outcomes (discrimination) and forecasting mortality (calibration) but with differing degrees of predictive accuracy in general ICU populations (Godinjak et al., 2016; Knaus, 2002; Salluh & Soares, 2014; Vincent & Moreno, 2010).

Moreover, the review of literature supported the premise that each model quantifies disease severity, determines prognosis, and guides therapeutic interventions. Nevertheless, optimal performance comparing APACHE II, SAPS II, and SOFA within the ICU oncology sub-population remained to be determined. A more in depth appraisal of the literature (i.e., systematic review) and synthesis (i.e., meta-analysis) was an opportunity to answer the primary research question. The process involved focusing solely on research dedicated to APACHE II, SAPS II, and SOFA model applications in the critically ill cancer population. Conducting a meta-analysis in this area of research serves as a reference for CCNs and intensivists to explore how vPMs can be applied clinically when there is uncertainty, concerns about delivering futile care, and decision conflicts.

Chapter 3

Methods

The overall aim was to determine the predictive accuracy of each vPM by combining study results from previous investigations evaluating individual performances of vPMs. Follow up statistical analysis included pooling the data to compare overall performances to determine greatest predictive accuracy among the three vPMs: APACHE II, SAPS II, and SOFA. No human subjects were under investigation and no related ethical considerations were involved in the process.

Research Questions

The following questions were addressed in this study:

1. Which prognostic scoring system performs 30-day mortality predictions most accurately for critically ill cancer patients admitted to the ICU?
2. Among the study sample, what physiological variables are reported to be additional independent predictors of 30-day mortality for oncology patients in the ICU?

Design

A meta-analysis using meta-regression with random-effects model to combine and summarize the results of prognostic model validation studies was the study design. Validation studies are the main way to assess or validate the performance of a vPM on a new patient population. The design of validation studies are to compare predicted and observed mortality outcomes for groups of patients (calibration) and to quantify the model's ability to distinguish between patients who do or do not experience the event of interest (discrimination) (Moons et al., 2009). These studies tend to report performance outcomes in the form of AUCs.

Procedures

The meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria (see Figure 2, pg. 45) (Liberati et al., 2009). An extensive search of the literature for studies with similar performance aims (i.e., validating predictive accuracy when computed within the first 24 hours of admission) were conducted using the following search procedure. Literature searches of CINAHL, PubMed, Web of Science, and Cochrane Library databases spanning January 2000 to February 2017 timeframe were completed. Each literature search was limited to articles reporting critically ill oncology patients as the study population and admitted to the ICU setting. Study participants in articles of interest were confined to study populations admitted to the ICU for management associated with cancer-related diagnoses.

The search included prospective and retrospective observational cohort studies using the following key words and medical subject heading (MeSH) terms: "Acute Physiology and Chronic Health Evaluation II (APACHE II)" "Simplified Acute Physiology Score (SAPS)", and "Sequential Organ Failure Assessment (SOFA)" with subheading "oncology", "cancer", "ICU" and its derivates, "critically ill", "prognostic model", "prognostic scoring system", "severity-of-illness scores", "prognosis and outcome", "prediction" and "mortality". Search terms combining key words with "AND" and "OR" were added for broader searches. Studies were full-text English-language, peer-reviewed articles published between January 2000 and February 2017. To identify additional studies, reference lists of all eligible articles were examined, crosschecked, and included if eligibility requirements were met.

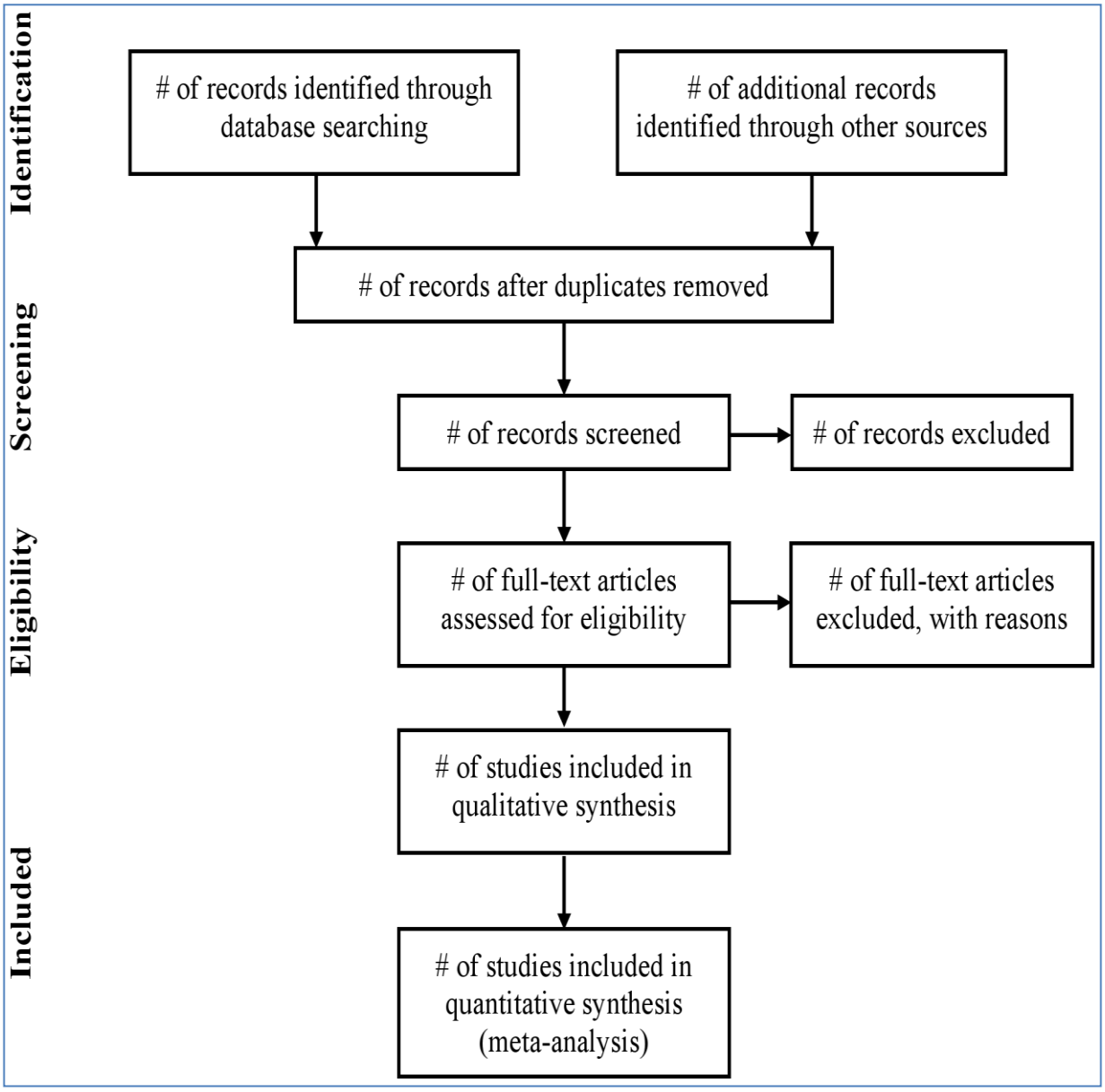

Figure 2. PRISMA Flow Diagram

Reference: Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed.1000097

Data Extraction and Collection

Data extraction followed the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of prediction Modeling Studies (CHARMS) protocol (Figure 3) (Moon et al., 2014). Data collection involved the use of study-level data instead of individual-level data.

Study-level data collected were the performance results of APACHE II, SAPS II, and SOFA models reported in peer-reviewed literature. Study-level data analyzed refers to the diagnostic performance statistics, AUCs (see "Definition of Terms") with standard error of the estimates (SE), reported in each eligible study.

Area under the characteristics curve was used for data extraction because it represents the degree of concordance between vPM prediction and observed mortality in the study population. An AUC of 0.70 to 79 is "fair performance" with AUC 0.80 to 0.89 and 0.90 to 1.0 representing "good performance" and "excellent performance", respectively. Including SEs with its corresponding AUC accounted for the standard deviations in each study sampling distribution.

Checklist Item	**Example**
✓ 1. Prognostic versus diagnostic prediction model?	The aim is to predict future events The aim is to detect disease status
✓ 2. Intended scope of the review?	Models to inform therapeutic decision-making Models to inform referral or transfer patient
✓ 3. Type of prediction modelling studies?	Prediction model development with external validation External model validation only
✓ 4. Target population?	Patients with cancer Patients with out-of-hospital cardiac arrest
✓ 5. Outcome to be predicted?	Specific future event such as "in-hospital" mortality Specific disease status such deep vein thrombosis

✓ 6. Time span of prediction?	30-day ICU mortality 31-day to 6 month mortality
✓ 7. Intended moment of using the model?	Models to be used upon admission to the ICU from ER Models to be used post-operatively in ICU

Figure 3. CHARMS Key Items Checklist to Guide Systematic Review Process.

Based on Moons, K. G. M., et al. (2014) Critical appraisal and data extraction for systematic reviews of prediction modelling studies: The CHARMS Checklist. PLoS Med 11(10): e1001744. https://dx.doi.org/10.1371/journal.pmed.1001744

The sample included studies focused on the prognostic performance of APACHE II, SAPS II, and SOFA models in the ICU-based adult oncology patient population. The shared aim across studies was to validate vPMs ability to discriminate between patients who lived from those who died. Model performances were based on discrimination (see "Definition of Terms") calculated within the first 24 hours of admission and endpoint was 30-day ICU mortality. Each study included in the meta-analysis reported the AUC as its measure of discrimination. A study was excluded if information was insufficient for data extraction.

To address the secondary research question, articles eligible to answer the primary research question were reviewed for additional discussions centered on single physiological variables explored for a relationship to ICU mortality. Physiological variables of interest were limited to covariates in which univariate analyses were performed to detect a statistically significant ($p < 0.05$) influence on ICU mortality. The intent was to identify and describe physiological variables not captured in vPM algorithms but were found to be associated with 30-day ICU mortality risk.

The principle investigator independently reviewed and extracted data from eligible studies entered into a Microsoft Excel spreadsheet. Demographic data included information such

as first author, year of publication, country of origin, sample size, setting, cancer type, study time period, and study type. Specific performance-related data extracted included AUCs, standard errors [SE], 95% confidence intervals, Hosmer-Lemeshow goodness-of-fit p value, and estimation of mortality. To ensure data entry accurateness, data were cross-checked and final recheck procedure was conducted prior to statistical analysis.

Statistical Analysis

Inferential statistical analyses were performed using MedCalc for Windows version 17.2 statistical software package (MedCalc Software, Ostend, Belgium). The AUCs with SE were extracted from each study to calculate pooled AUCs to answer the primary research question. When an SE for an AUC was not provided in a study, the reported number of survivors and non-survivors were used to estimate it with methods described by Hanley and McNeil (1982). Publication bias was analyzed using Egger's test (Egger et al., 1997) and displayed graphically with a funnel plot.

To Test Heterogeneity

Statistical analyses were conducted on study-level data extracted from the eligible articles. Meta-regression using random-effects model to test heterogeneity was performed on this data to determine pooled AUCs results for APACHE II, SAPS, and SOFA. Summarizing pooled AUCs provided a more precise estimate of model performance for each vPM (Haidich, 2010). When heterogeneity is present, summary measures must be interpreted within the context of understanding the nature of variability in and across the studies. Statistical heterogeneity is implicit because the performance outcomes in the studies are untenable.

There was also the assumption of no single true effect (i.e., the outcome in each study is the same) due to variations in the characteristics of study populations and methodologies applied

from study to study. The premise is that clinical and methodological diversity increases the chances of statistical heterogeneity (Preuss & Ziegler, 2014). Therefore, random-effects modeling was applied because it assumes 1) variability in study designs, 2) that differences in underlying study populations exist, and 3) outcomes will vary across studies.

First, data was grouped according to prognostic model and then random-effects modeling was added to statistical analysis to account for between-study variance (τ^2). The random variation within the studies plus the variation between the different studies was addressed using this method. In random-effects modeling, the study variance is inversely weighted with the heterogeneity parameter (Cochran's Q test and Higgins I squared statistic) (Haidich, 2010; Preuss & Ziegler, 2014). The summary weighted mean effect (i.e., weighted performance mean for APACHE II, SAPS II, and SOFA) was then generated so that a pooled analysis would determine greatest predictive accuracy among the three vPMs.

The heterogeneity of the pooled AUCs was measured using Cochran's Q test and Higgins I squared (I^2) statistic. Statistical significance for the Q test was defined as $p < 0.1$ (because of low power) and $I^2 > 50$ percentage. Statistical heterogeneity was expected because of the methodological differences between the vPMs involved in making mortality predictions. For example, the models differ in number and predictor variables such as the SAPS II uses blood urea nitrogen versus SOFA uses serum creatinine to represent renal function. However, the vPMs measure the same three physiological variables which are Glascow Coma Score for neurological assessment and partial pressure of O2 in arterial blood [paO_2] with fraction of inspired oxygen [FiO^2]) to determine tissue oxygenation.

In summation, the random-effects model in this study produced a distribution of true effects (a series of AUCs) with no missing data for all studies in each vPM group. The random-

effects model combined true effects of these studies to estimate the weighted mean performance because of τ^2 in each group distribution. This process resulted in summary AUCs for APACHE II, SAPS II, and SOFA with single-value pooled estimates of the weighted mean performance (i.e., mean distribution of AUCs) for each model distribution. After generating summary AUCs, the pooled effects of APACHE II, SAPS II, and SOFA performances were compared to determine the vPM with greatest predictive accuracy.

Chapter 4

Results

The selection process using PRISMA criteria is shown below (Figure 4). Initially, 227 published articles were identified using the first search strategy. After screening titles and abstracts, 57 potential studies were reviewed in full-text format. After reading these studies, 22 eligible validation studies met the inclusion criteria.

Description of Sample

A minimum of 10 studies for each vPM was sought to obtain meaningful interpretations to support an evidence-based conclusion (Borenstein et al., 2009). The search yielded 22 validation studies reporting performance outcomes for the three vPMs in the critically ill oncology ICU sub-population. Among the 22 validation studies, there were 16 articles, 15 articles, and 8 articles reporting AUCs for APACHE II, SAPS II, and SOFA models, respectively. Some studies included more than one group of study subjects who underwent mortality risk estimation by more than one vPM. As a result, the search yielded a total of 21 reported AUCs for APACHE II, 18 AUCs for SAPS II, and 10 AUCs for SOFA (see Appendix E).

Key characteristics of the identified studies analyzed are shown in Appendix F. Together, the 22 validation studies comprised 13 countries spanning four continents (Asia, Europe, North America, and South America) and the Middle East. Study periods spanned the 1990s to 2011 in 228 hospitals with two independent studies conducted at one hospital in Mexico during the same time-period. There were four categories of hospitals identified – university, university-affiliated oncology specialty, tertiary oncology specialty, and tertiary community. All studies (12 retrospective cohorts, 10 prospective cohorts and one combined retrospective and prospective

cohort) were set in adult medical and surgical ICUs. Eleven ICUs were dedicated to treating oncology-only patients.

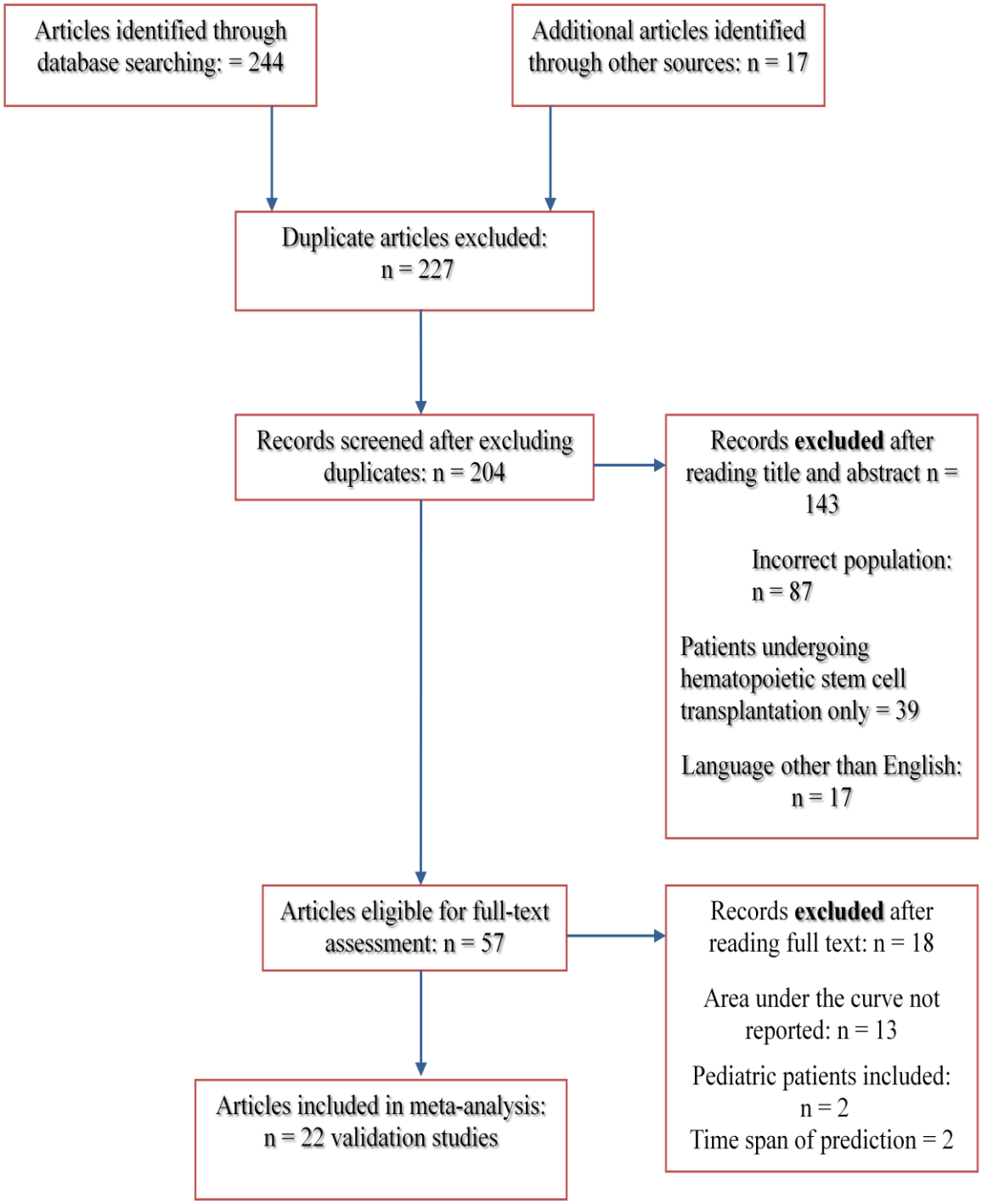

Figure 4. Flow Chart Of Literature Selection

A majority of the studies were validation studies testing the performance of the vPMs. There were three out of the 22 validation studies that included testing a new model (model development) while comparing the performance with established vPMs. Sixteen studies reported findings for APACHE II (73%), 15 studies included SAPS II (68%), and 8 studies (36%) measured SOFA performance. A combined 14,644 patients with 25 cohorts (three studies had two separate groups) comprised this study. The sample sizes ranged from 50 to 7,689 adult oncology ICU patients. The oncology patient mix was 10 solid/hematological cohorts, three hematological malignancies cohorts, three colorectal cancer cohorts, two solid tumor cohorts, and one cohort each for: Acute Myeloid Leukemia, Acute Myeloid Leukemia with Non-Hodgkins lymphoma, gastric cancers, and gynecological cancers.

Some validation studies reported AUCs for two or more models. Other studies reported AUCs for more than one sample population. This resulted in the performance of a vPM sometimes reported more than once in an article to represent predictions performed on different patient groups in the study (see Appendix E). For example, Cardenas-Turanzas et al (2012) conducted a validation study evaluating the performance of SOFA in two cohorts: n = 540 medical ICU oncology patients and n = 783 surgical ICU oncology patients. The SOFA performance was an AUC of 0.79 (0.024 SE) in the medical ICU group and 0.79 (0.063 SE) in the surgical ICU group.

Models and Predictions in the Sample

In totality, there were 32,303 combined predictions performed among the three vPMs in this meta-analysis. In the APACHE II cohort group, 16,764 mortality predictions were tested for predictive accuracy across 22 validation studies. Among the SAPS II and SOFA cohort groups, the models made 12, 960 (18 articles) and 2,579 (10 articles) total predictions, respectively. The

combined findings from all predictions led to sorting outcomes into three groups of pooled estimates to best summarize the overall performances of APACHE II, SAPS II, and SOFA models.

Models Performance Statistics

For this study, the focus was on the discriminating power of vPMs. As stated earlier, discrimination refers to a model's ability to make predictions by differentiating between 30-day ICU survivors and 30-day ICU non-survivors with accuracy. It is reported via the AUC, which is expressed in the form of a correlation coefficent ranging from 0 to 1. Discrimination, measured by AUCs, for APACHE II (n = 16,764 predictions) ranged from 0.60 to 0.94 with 0.80 mean (95% CI 0.761 to 0.848, 0.095 SD, SEM 0.021, variance 0.008). Discrimination for SAPS II (n = 12, 960 predictions) ranged from 0.67 to 0.92 with 0.792 mean (95% CI 0.760 to 0.824, 0.063 SD, SEM 0.015, variance 0.004). Discrimination for SOFA (n = 2,579 predictions) ranged from 0.68 to 0.91 with 0.785 mean (95% CI 0.735 to 0.834, 0.069 SD, SEM 0.021, variance 0.004).

The data comes from different studies and diverse populations resulting in the need to perform a goodness-of-fit test to account for potential discrepancies between predicted and observed outcomes. The D'Agostino-Pearson to test for normal distribution of the true effects (AUCs) was $p = 0.467$ ($p > 0.05$, accept normality) for the APACHE II model overall performance in validation studies (Sheskin, 2011). The D'Agostino-Pearson test for SAPS II and SOFA models overall performances were $p = 0.983$ and SOFA was $p = 0.837$, respectively. Results of the D'Agostino-Pearson test indicate all models had normal distributions.

Independent samples t-test for assumption of homogeneity of variances was tested between APACHE II and SAPS II model groups and APACHE II and SOFA model groups. Homogeneity of variances was satisfied via *F* test for equal variances ($p = 0.364$). Considering

there were unequal numbers in each cohort, the Welch test was performed for unequal variances, F (23.4) = - 0.565, two-tailed p = 0.577. These steps were repeated between SAPS II and SOFA model groups. Homogeneity of variances was satisfied via F test for equal variances (p = 0.738). Welch test for unequal variances showed F (17.5) = 0.271, two-tailed p = 0.789. The results were non-significant confirming no difference between the means of the three model groups.

Because the vPMs use different, yet similar combinations of physiological variables to predict mortality, there was an assumption of independence among the performances of the three models. Pearson product-moment correlation coefficient was computed to assess the relationship between APACHE II and SAPS II. There was no correlation between the two models (r = -0.016, p = 0.950). This step was followed by examining the relationship between APACHE II and SOFA. This also showed no correlation between the two models (r = -0.185, p = 0.608). The SAPS II and SOFA showed greater correlation (r = 0.290, p = 0.608) but lacked statistical significance. This implies the vPMs are independently, discrete from one another.

Heterogeneity Testing

As stated earlier, meta-regression to test heterogeneity using random-effects model was performed on study-level data to determine the summary AUCs for APACHE II, SAPS II, and SOFA. The random-effects model (Zhou et al., 2002 method) was used to analyze the pooled AUCs because heterogeneity was significant for all 3 vPMs (see Table 5) and the study sample observed outcomes were expected to be varied. Statistical significance for the Q test was found (Q = p < 0.001) and Higgins I^2 was > 50 percent for all three vPMs.

Results of the Q test and Higgins I^2 confirm substantial heterogeneity for all cohorts. Together, the Cochran Q test of homogeneity (p = < 0.0001) with Higgins I^2 (> 50%), which quantifies the degree of heterogeneity, determined the studies were not homogeneous. The

results showed true heterogeneity between studies for APACHE II (I^2 = 94.56%), SAPS II (I^2 = 94.66%), and SOFA (I^2 = 80.21%). These finding were expected because the studies were not from a common population.

Table 5.
Test of Heterogeneity

vPM Cohort	Cochran's Q test*	DF	Significance level	Higgins I^2 (inconsistency)**	95% CI for I^2
APACHE II	367.4632	20	P < 0.0001	94.56%	92.85 to 95.86
SAPS II	318.3987	17	P < 0.0001	94.66%	92.83 to 96.02
SOFA	45.4760	9	P < 0.0001	80.21%	64.42 to 88.99

*Q is the weighted sum of squares on a standardized scale. It is reported with a p value with low P-values indicating presence of heterogeneity. I^2 is the percentage of observed total variation across studies that is due to real heterogeneity rather than chance. It is calculated as I^2 = 100% x (Q - df)/Q. A value of 0% indicates no observed heterogeneity and larger values show increasing heterogeneity.

A meta-regression requires weight be assigned to each pooled study. Cochran's Q is the weighted sum of squares and reflects the total dispersion of studies around the grand mean. Each Q statistic was evaluated with respect to its degrees of freedom and the weighted pooled studies are graphed in forest plots (Figures 5, 6 and 7). To the left of each forest are the studies reporting the AUC for the respective cohort group. The studies are listed alphabetically and repeated when 2 or more AUCs are reported in its outcomes. Each study is represented by a filled square to denote its AUC and the horizontal line signifies the corresponding 95% confidence interval. The diamond at the bottom of each graph is the pooled estimated mean performance and width reflects the precision of that estimate based on random-effects modeling.

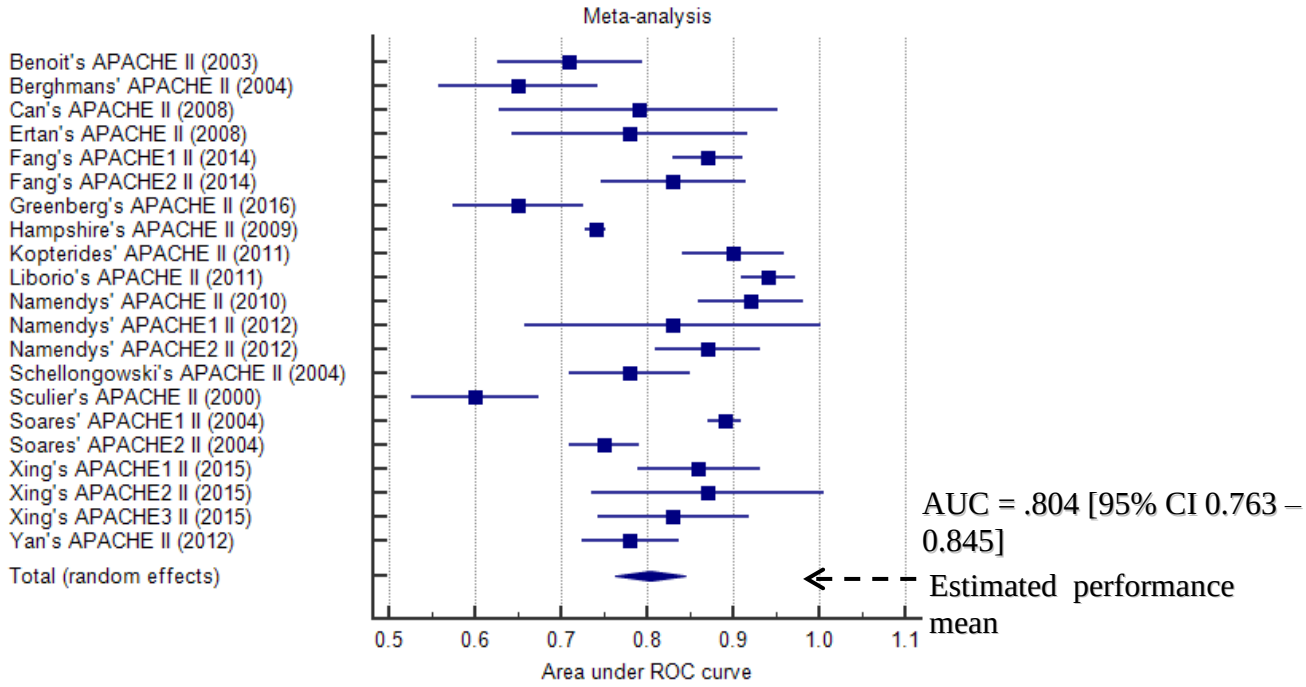

Figure 5. APACHE II Cohort: Pooled Weighted Studies

Liborio et al. (2011) prospective study (n = 288, hematological/solid cancer) with oncology only MSICU patient mix performed best in the APACHE II cohort with AUC 0.940. Sculier et al. (2000) had the worst performing study (n = 261, hematological/solid cancer) with oncology only MSICU patient mix reporting an AUC of 0.60.The overall pooled magnitude of weighted effect in this cohort was 0.804 (95% CI 0.763-0.845).

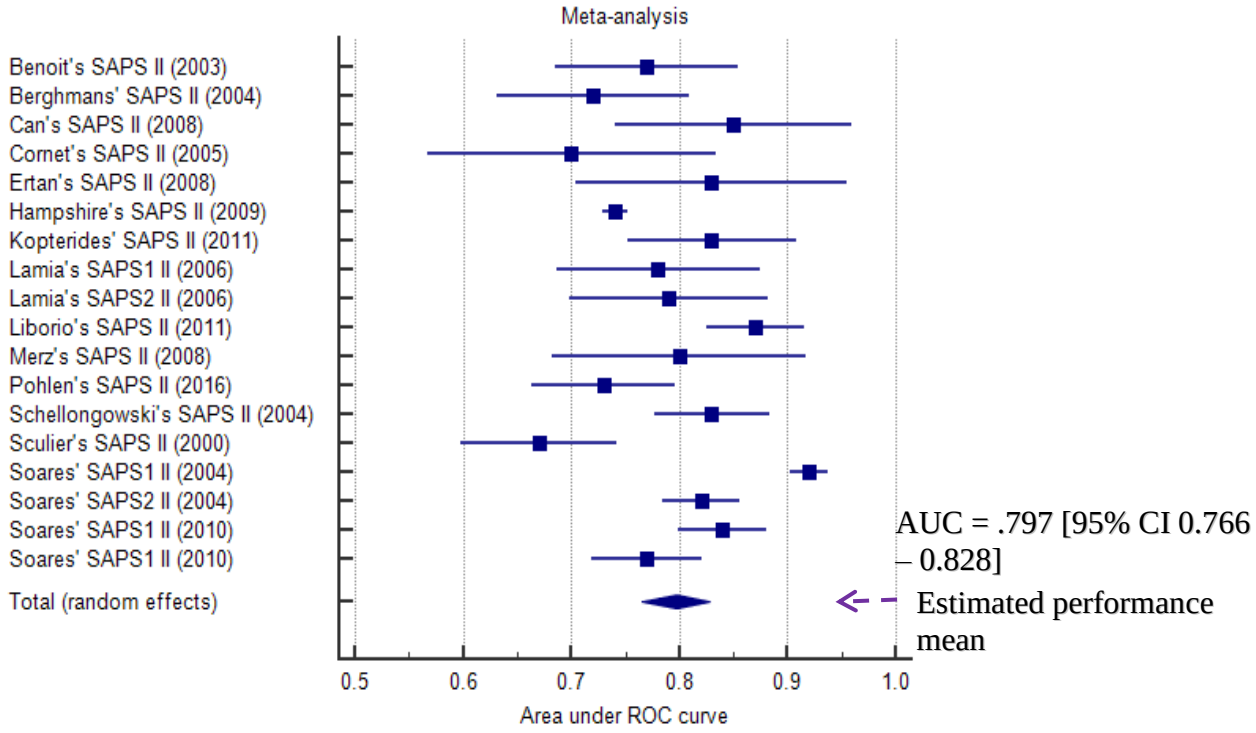

Figure 6. SAPS II Cohort: Pooled Weighted Studies

Soares et al. (2004) prospective study (n = 1,257 patients with hematological/solid cancers) in a MSICU performed best in the SAPS II cohort with AUC 0.916. Sculier et al. (2000) prospective study had the worst performing outcome (n = 261, hematological/solid cancer) for SAPS II with oncology only MSICU patient mix reporting an AUC of 0.67.The overall pooled magnitude of weighted effect in this cohort was 0.797 (95% CI 0.763-0.845).

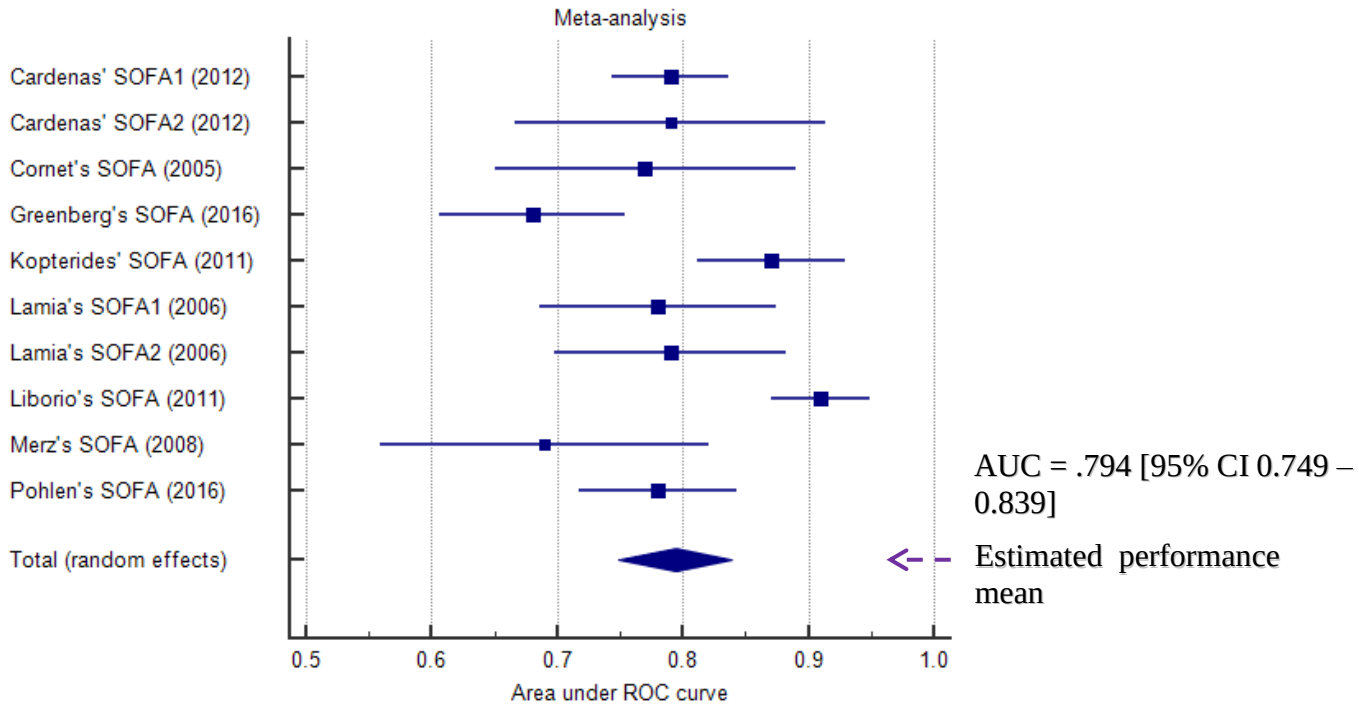

Figure 7. SOFA Cohort: Pooled Weighted Studies

Liborio et al. (2011), prospective study (n = 288 patients with hematological/solid cancers) in a MSICU performed best in the SOFA cohort with AUC 0.910 while the overall pooled magnitude of effect in this cohort is 0.794 (95% CI 0.749 – 0.839). Greenberg et al. (2016) had the worst performing study (n = 245, hematology cancers) with an AUC of 0.65 that was conducted retrospectively in a MICU. This model was being compared to a development model in the primary study.

The pooled or summary AUCs for APACHE II, SAPS, and SOFA were 0.804, 0.797, and 0.794, respectively (see Table 6). The APACHE II demonstrated good discrimination while SAPS II and SOFA showed fair discrimination. The fixed-effect model was invalid because heterogeneity was significant for all three vPMs and confirmed why random-effects modeling was selected (see Table 5). The random-effects AUCs were then compared (APACHE II with SAPS II, $p = 0.7897$, APACHE II with SOFA $p = 0.7471$, SAPS II with SOFA $p = 0.9147$) for all models. The findings led to the statistical conclusion that the performances of AUCs for the three cohorts are not significantly different; therefore, the weighted performance means are similar.

Table. 6.
Summary AUC with Random-Effects Model

vPM Cohort	Summary AUC (random effects)	Standard (SE)	*P* value	95% CI	Summary AUC (fixed effects)	Standard (SE)	95% CI	*P* value
APACHE II	0.804	0.0208	<0.001	0.763 to 0.845	0.797	0.00422	0.789 to 0.805	<0.001
SAPS II	0.797	0.0160	<0.001	0.766 to 0.828	0.798	0.00425	0.790 to 0.806	<0.001
SOFA	0.794	0.0230	<0.001	0.749 to 0.839	0.821	0.0108	0.800 to 0.842	<0.001

The pooled Area under the ROC curve with 95% CI is given both for the Fixed effects model and the Random effects model.

Accounting for Bias

Publication bias is a threat to the validity of clinical research, which can distort the totality of the available evidence on a research question. This can lead to misleading inferences in systematic reviews and meta-analyses (Haidich, 2010). The Egger's test was performed to detect publication biases (e.g., only publishing studies with favorable outcomes), which were depicted graphically using funnel plots. There are more than 10 articles with statistically significant findings in each study included in this meta-regression, making it appropriate for testing (Egger et al., 1997; Sterne & Egger, 2001).

Funnel plots are displayed below for each cohort of vPM studies (Figures 8, 9, and 10). The unfilled circles are plotted according to the reported AUCs (x-axis) and corresponding SEs (y-axis). Two diagonal lines represent (pseudo) 95% confidence limits (effect ± 1.96 SE) around the summary effect for each standard error on the vertical axis. If publication bias is present, the funnel plot will be asymmetrical.

Both APACHE II (Figure 8) and SAPS II (Figure 9) cohorts showed symmetry. The SOFA cohort (Figure 10) was expected to be vulnerable to bias due to the smaller number of studies (low statistical power) included in this model cohort. It is asymmetrical because the majority of the AUCs are not evenly dispersed in the funnel; rather, they collected to the left of 0.8 median. Low statistical power in the presence of heterogeneity can lead to false claims of publication bias (Loannidis & Trikalinos, 2007). The SOFA cohort was asymmetrical implying publication bias. However, smaller number of studies (n = < 10) tend to show larger effects that mimic bias and reduced heterogeneity may be exaggerated by the small sample size.

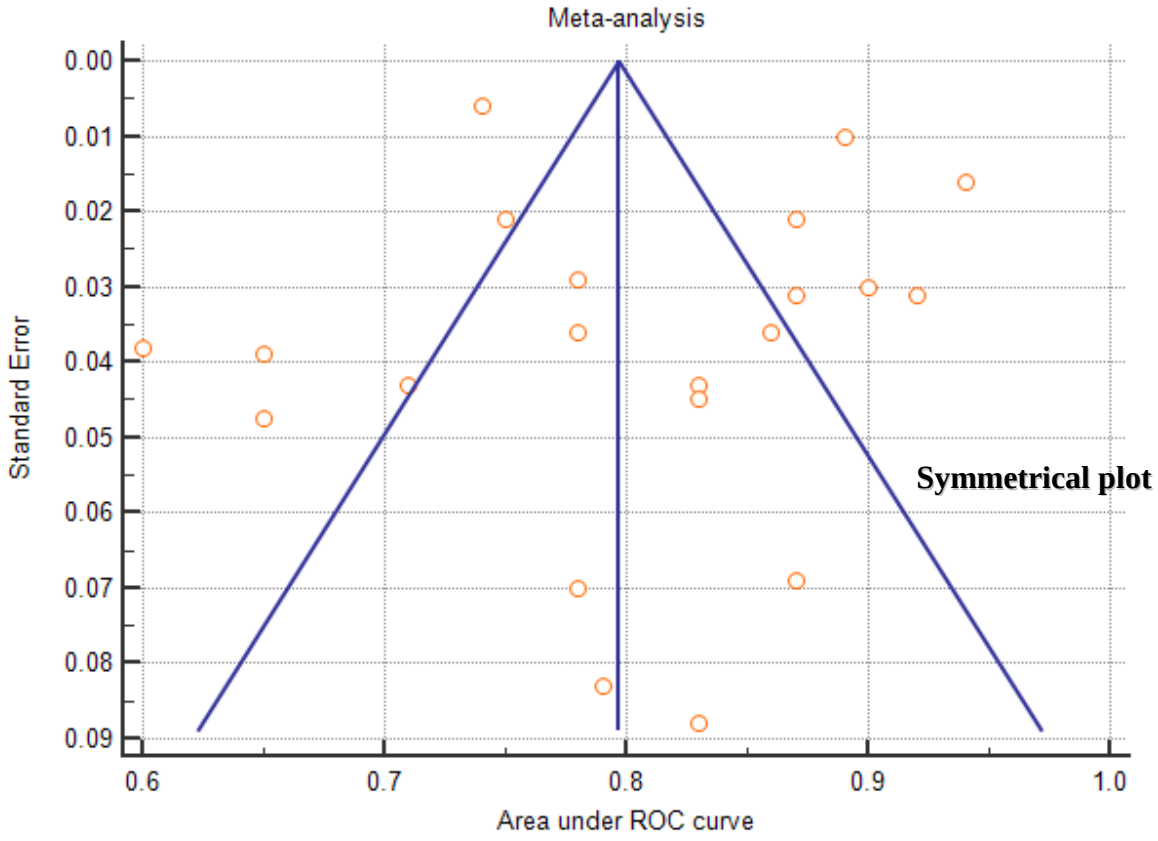

Figure 8. APACHE II Funnel Plot Asymmetry Test

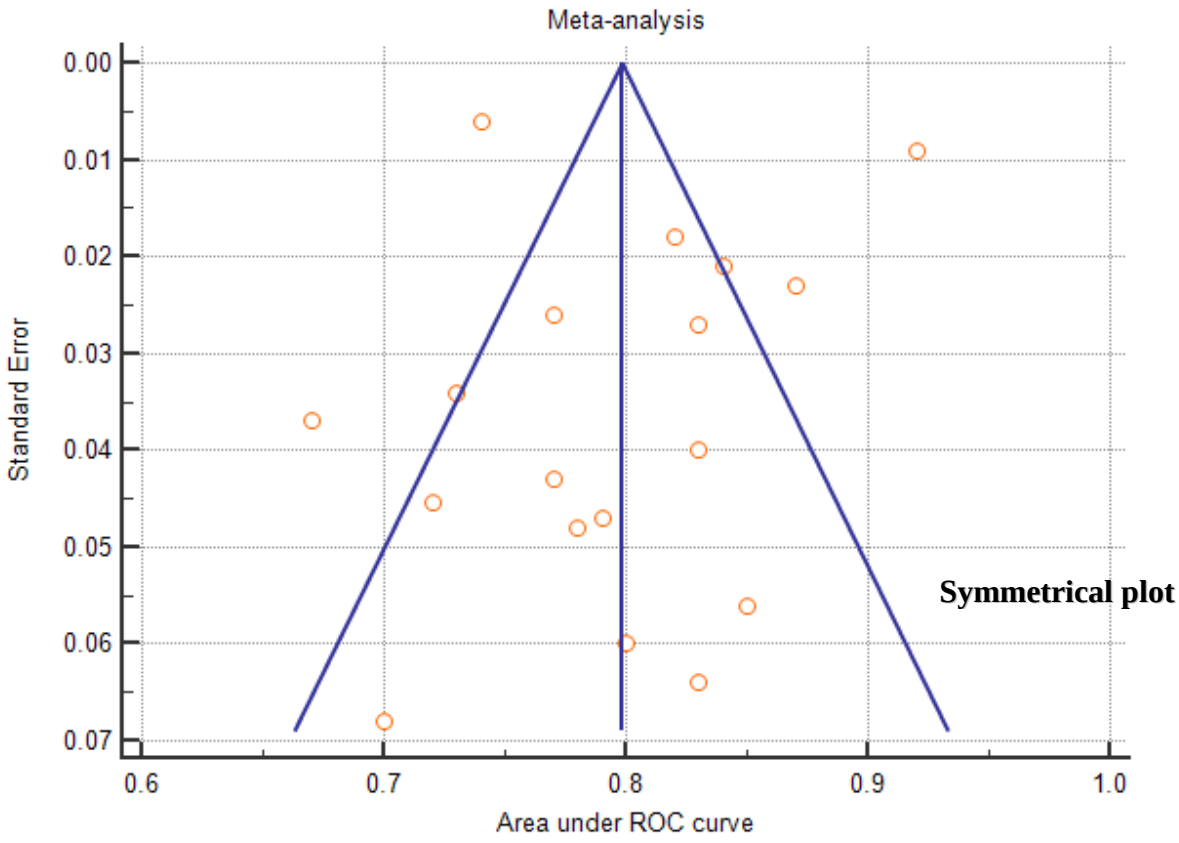

Figure 9. SAPS II Funnel Plot Asymmetry Test

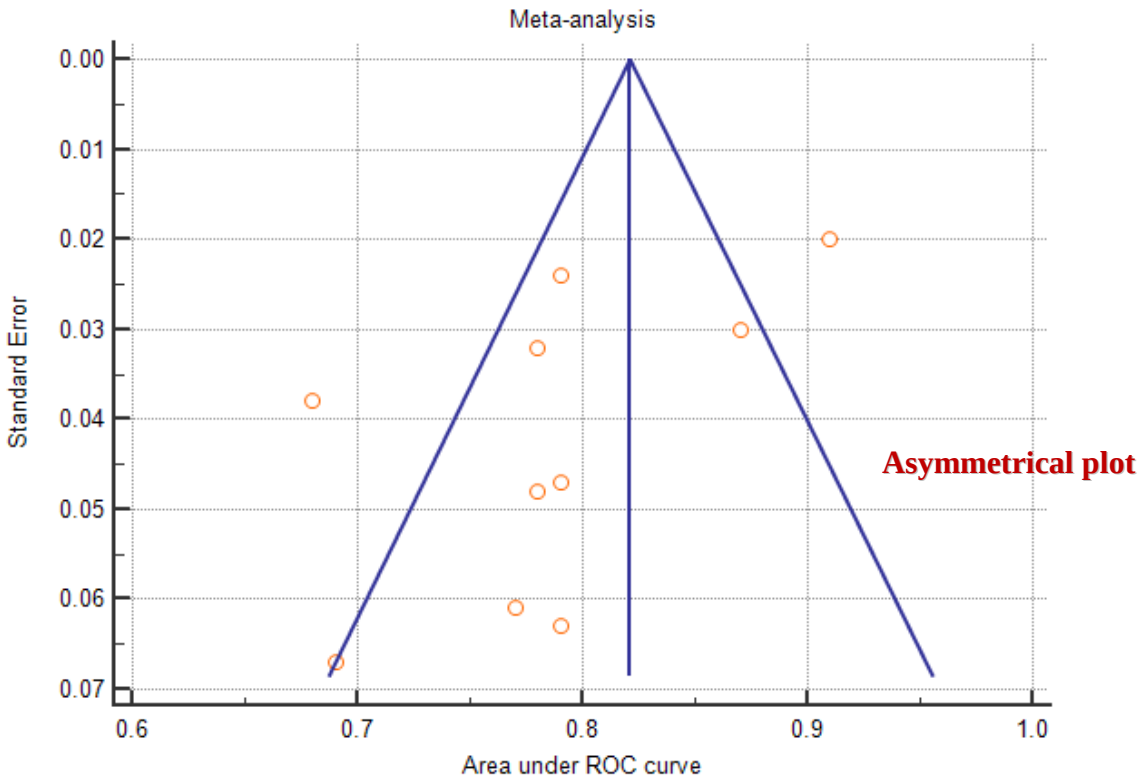

Figure 10. SOFA Funnel Plot Asymmetry Test

Independent Predictors of Mortality

The secondary aim of the study was to identify independent predictors of mortality measured and reported in the 22 eligible validation studies. Physiological variables of interest were limited to physiological covariates in which univariate analyses were performed to detect a statistically significant ($p < 0.05$) influence on ICU mortality. The intent was to identify and describe physiological variables not captured in vPM algorithms and were associated with 30-day ICU mortality risk.

Physiological variables identified as independent predictors, but already measured in a model, were not included in data extraction. As a result, the inquiry yielded no results. For

example, Benoit et al. (2003) identified requiring intubation within the first 24 hours of admission, serum creatinine > 1.2, and blood urea nitrogen > 0.75, leucopenia, and the use of vasopressors as prognostic indicators of 30-day ICU mortality. These variables are already measured in the vPMs; therefore, offer no meaningful insights for this type research question. The most frequently occurring independent prognostic indicator of mortality risk was the use of vasopressors, which is measured in the SOFA model.

In the Soares et al. (2004) study (n =1,257), APACHE II (AUC 0.89) and SAPS II (0.92) showed good to excellent discrimination without independent prognostic variables explored in the analysis. The Liborio et al. (2011) study (n = 288) also showed good (SAPS II, AUC 0.869) and excellent (APACHE II, AUC 0.940; SOFA, AUC 0.910) discrimination. In this study, the authors identified 13 physiological variables that increased risk for hospital mortality but the models also address these predictors. After surveying the articles, there was insufficient data to analyze, summarize, or describe independent predictors associated with 30-day ICU mortality not captured in the vPMs.

Chapter 5

Summary

The approach chosen to determine the vPM most suitable for the critically ill cancer population was a meta-analysis using meta-regression with random-effects modeling technique. Study-level data were extracted from prospective and retrospective cohort-type validation studies aimed at the predictive accuracy of APACHE II, SAPS II, and SOFA models. After applying PRISMA criteria to the literature search, 22 articles met eligibility criteria. The CHARMS protocol guided data extraction. Together, PRISMA criteria and CHARMS protocol was a structured approach to organizing the steps to answering the research questions and reporting the outcomes.

Systematically reviewing the literature provided a sufficient amount of data to generate diagnostic performance statistics. The processed yielded 32,303 combined predictions performed among the three vPMs. The APACHE II, SAPS II, and SOFA cohort groups performed a total of 16,764, 12,960, and 2,579 mortality predictions respectively. Predictive accuracy for APACHE II ranged from 0.60 to 0.94 (0.800), SAPS II 0.67 to 0.92 (0.792), and SOFA 0.68 to 0.91 (0.794) across the 22 validation studies.

Random-effects accounted for between-study variance and heterogeneity, resulting in a weighted mean for individual studies and pooled mean effects. Study weights led to APACHE II cohort performance mean increasing slightly to 0.804 from the 0.800 after accounting for heterogeneity. The SAPS II cohort performance mean increased to 0.797 when compared to the 0.792 before random-effects modeling. The SOFA cohort improved most with an initial 0.785 that changed to 0.794 performance mean effect. The conclusion is APACHE II demonstrated good discrimination while SAPS II and SOFA showed fair discrimination.

The overall performance means for APACHE II, SAPS, and SOFA were 0.804, 0.797, and 0.794, respectively. Based on the findings, the APACHE II demonstrated greatest predictive accuracy when compared to SAPS II and SOFA models. Although APACHE II performed best, clinical significance is not established based on these findings. Measures of correlation among vPMs demonstrated no relationships between the models. Adjunct to vPM research, no independent predictors of to 30-ICU mortality were identified in this study.

Discussion

Diversity among researchers tends to lead toward different approaches to investigating important questions. In this study, examining previous works centered on questions about the performances of vPMs in the ICU wasdeemed important to delivering quality bedside care. The varying approaches to uncovering the answer to vPM performances created an opportunity to integrate the findings from multiple independent studies to inform evidence-based practice. Similarities in methodologies and aims centered on the vPM performances in the critically ill oncology population resulted in independent studies being aggregated using statistical procedures to quantify significance to bedside care.

Sample

Following PRISMA guidelines, this study was a systematic attempt at quantifying the results of independent research to gain evidence-based knowledge that will further guide clinical practice. A limitation of this approach is study-level data. In contrast to data at the subject-level, study level data is restricted to information available for extracting from independent reporting of findings. Issues such as individual study bias, design flaws, and improper data collection techniques cannot be managed using the methodological approach in this study. Nevertheless,

the random-effects models accounted for heterogeneity associated with differences in characteristics of studies and study populations.

The CHARMS protocol added scientific rigor because it pre-specified the objectives and methods of data extraction. The study sample was limited to validation studies that were testing vPMs performances in new populations (i.e., oncology patients) to determine if clinical validity was maintained in specific patient groups. A strong point of this approach is the ability to isolate the performances in a group for analysis. The limitation of this approach was the lack of model performance comparisons with performances in general ICU populations. Whether or not the models perform better in the general population remains unknown.

Following the CHARMS protocol restricted post hoc decisions during the review process; thus limiting bias such as selective outcome reporting. Publication bias is a concern for publishing only studies that demonstrate favorable outcomes. The Egger's test showed no publication bias associated with the APACHE II and SAPS II cohorts. The AUC performances in each group varied: 0.60 to 0.94 (APACHE II), 0.67 to 0.92 (SAPS II), and 0.68 to 0.91 (SOFA). The APACHE II cohort demonstrated the widest range gap (0.34) and SOFA had the narrowest range gap (0.23). The small sample of studies identified for the SOFA model can be attributed low statistical power and reduced heterogeneity.

Primary Study Aim

A validated prognostic model performance is related directly to the ratio between accurate predictions and observed outcomes when establishing legitimacy for bedside application. In this study, APACHE II performed with greatest accuracy but had significantly more predictions in comparison with the other models. It is the gold standard among vPMs, which can be attributed to the availability of more studies and greater reporting of prediction

events. The least performing vPM, SOFA, had significantly fewer predictions because of fewer published studies available for statistical analysis. The SAPS II model's overall performance was closer to APACHE II, which coincided with a comparable number of prediction events.

The strength of using meta-regression to summarize the findings of multiple studies is its scientific approach. It objectively reduces conflict and ambiguity associated with examining the evidence based solely on case-by-case analysis. A key limitation is the grouping of performance assessed based on study-level data. In this study, the data is based on model overall performance (i.e., mean) as reported in individual studies rather than scrutiny of performance at the individual level. Predictive accuracy cannot be stratified using study-level data.

Individual level data is more appropriate for observing performance differences representative of physiological extremes and gray areas. For example, a vPM performance among terminally ill patient populations is probably greater than 0.9 (i.e., excellent discrimination). Likewise, vPM performance for patients admitted for low acuity needs such as observation status is also favorable towards high predictive accuracy. Evidence supporting the validity of vPMs are important to the bedside nurse and physician. However, research of prognostic models outcomes among cancer patients with clinically ambiguous situations may be more meaningful. As a result, predictions that are objective for oncology patients who fall in the uncertainty category still need to be addressed in future research.

Secondary Study Aim

The secondary aim of the study was the identification of independent predictors of ICU mortality not included in APACHE II, SAPS II, and SOFA models. The impetus for this exploration was to gain new insights into routinely measured physiological variables that may improve the predictive performance of any widely accepted vPM. Identifying independent

predictors of mortality are important to clinical nursing because early warning signs are a part of critical thinking and anticipatory care in nursing practice. After surveying the articles, there was insufficient data to analyze, summarize, or describe independent predictors associated with 30-day ICU mortality not captured in the models.

Ongoing investigation is required to determine independent predictors of mortality, not measured in the models. Restricting the search of independent predictors to reporting along with model performances was a limitation of this study. Conducting a meta-analysis of independent predictors may better address the secondary aim. This is more salient when examined in the context of the primary findings. That is to say, the main effects of vPMs in this study ranged from fair to good discrimination (0.0794 – 0.804). Identifying covariates that better capture the unique physiological challenges associated with cancer and its related treatment must be investigated to determine if the overall performance of model predictions can be improved to $\geq$ 0.90 in this population.

Conclusion

As the gold standard among vPMs, APACHE II performed with greatest predictive accuracy and achieved good discrimination ($\geq$ 0.80). Its combination of physiological variables, prediction algorithm and objectivity remained valid after scrutiny in this study. Heterogeneity was established across studies with no publication bias observed. Because the outcome is based on study-level data, ongoing research is need to explore the clinical significance and practical application of APACHE II in the critically ill oncology ICU sub-population. Pursuing clinical significance is an opportunity to examine feasibility, impact of use on staff attitudes, and application to decision-making at the bedside.

The overall performance was 0.804 for APACHE II. Nevertheless, a model that predicts at 0.9 or better (excellent discrimination) would be ideal. Because the model has not reached its full potential, the identification of additional physiological variables associated with ICU mortality using a different approach is warranted. In effect, identifying physiological variables most predictive of outcomes in the oncology patient will lead to the need to update current models. This includes adding variables representative of homeostasis, modifying algorithms, and ensuring that model changes improve performance and maintain objectivity.

Although SAPS II and SOFA did not perform as well, improving performance remains an important contribution to critical care management. A contributing factor to SOFA performance may be due to it being under-investigated in the cancer population. Cancer is one of the leading causes of death worldwide, but the overall number of articles retrieved was small relative to disease impact. Having a small number of studies to review was a limitation of conducting meta-analysis to answer both research questions. Limited information to support evidence-based practice supports continued nurse-led investigations centered on prognosis-related research.

Nursing Implications

The utility of prognostic models relies on capturing and documenting the physiological variables observed by CCNs during hemodynamic monitoring. These physiological variables function as prognostic factors by which the intensivists use the information to formulate a realistic clinical picture in collaboration with the bedside nurse. Together, the CCNs and intensivists use their expertise and practice scopes to demonstrate their collective investment in the well-being of the patient and assurance of delivering evidence-based, quality care. Therefore, future research should be centered on how prognostic information is shared at the bedside.

Prognosis research is central to addressing these types of issues in the clinical setting. Nurse-led research should focus on the contextual meaning of prognosis to the nurse and patient. Understanding its meaning will help CCNs better function as advocates during the decision-making process. Nursing investigation exploring vPM use as decision support aids have the potential to be far reaching. Particularly, nursing investigation should focus on the ICU setting because admission to the ICU is associated with anxiety and fears experienced among patients and family members; while nurses and physicians have concerns about delivering futile care.

Shared decision-making is a process and model use has implications for helping to reduce uncertainty experienced by patients, nurses, and physicians during a most critical time. Because prognosis involves two-way conversations, careful consideration for how vPMs are introduced into communication exchanges is important to advance nursing science. Explanations of prognoses should be undergirded by rich information delivered in a systematic, impartial, yet empathetic fashion but gaps in the literature exist about the role of nursing. This gap creates an opportunity for nurse-led investigation related to prognosis and nursing advocacy, education, and policy.

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Appendix A. Combination ICU Mortality Model

Use the *worst* value (US units) for each physiological variable within the past 24 hours.

VITALS				
HR	**BP**	**RR**	**Temp**	**GCS**
bpm	/ mmHg	bpm	C or F	

ARTERIAL BLOOD GAS			
pH	**pCO2**	**pO2**	**FiO2**
	mmHg	mmHg	%
Mechanical ventilation or CPAP	Yes	No	

CHEM-7				
Na	**K**	**CO2**	**BUN**	**SCr**
mEq/L	mEq/L	mEq/L	mg/dL	mg/dL
Acute renal failure	Yes	No		

Combination of APACHE II, SAPS II, and SOFA models to predict hospital mortality. Publically available at **http://clincalc.com/IcuMortality/Default.aspx**

Appendix A. Combination ICU Mortality Model (continued)

CBC		
WBC	**Hct**	**Plt**
x 10^9/L	%	x10^3/mm^3

MISC METRICS	
Urine output	mL per hour
Bilirubin	mg/dL
Vasopressors	No Yes
CHRONIC HEALTH	
Age	years
Chronic diseases	Metastatic cancer Hematologic malignancy AIDS
Type of admission	Scheduled (elective) surgical
Does this patient have severe organ system insufficiency or is immunocompromised? See definitions	No Yes
	Reset Calculate

Combination of APACHE II, SAPS II, and SOFA models to predict hospital mortality. Publically available at http://clincalc.com/IcuMortality/Default.aspx

Appendix B. Acute Physiology and Chronic Health Evaluation II

Use the *worst* value (US units) for each physiological variable within the past 24 hours.

Age	years
Glasgow coma score	
Vitals	
Temp	C or F
MAP	mmHg
Heart rate	bpm
Resp rate	bpm
Oxygenation	
FiO_2	%
PaO_2	mmHg
Arterial pH	
Chemistry	
Sodium	mEq/L
Potassium	mEq/L
Creatinine	mg/dL
Acute renal failure	No Yes
Hematology	
Hematocrit	%
WBC	x 10^9/L
Severe organ system insufficiency or is immunocompromised	No Yes
Reset Calculate	

APACHE II model to predict 30-day ICU mortality. Publically available at http://clincalc.com/IcuMortality/APACHEII.aspx

Appendix C. Simplified Acute Physiology Score II

Age	years
Vitals	
Heart rate	bpm
Systolic BP	mmHg
Temp	C or F
Glasgow coma score	
Oxygenation	
Mechanical ventilation or CPAP	Yes No
PaO_2	mmHg
FiO_2	%
Renal	
Urine output	mL per hour
BUN	mg/dL
Chemistry	
Sodium	mEq/L
Potassium	mEq/L
Bicarbonate	mEq/L
Bilirubin	mg/dL
Other	
WBC	x 10^9/L
Chronic diseases	Metastatic cancer Hematologic malignancy AIDS
Type of admission	Scheduled surgical

SAPS II model to predict 30-day ICU mortality. Publically available at http://clincalc.com/IcuMortality/APACHEII.aspx

Appendix C. Simplified Acute Physiology Score II (continued)

Use the *worst* value (US units) for each physiological variable within the past 24 hours.

Reset Calculate

SAPS II model to predict 30-day ICU mortality. Publically available at **http://clincalc.com/IcuMortality/APACHEII.aspx**

Appendix D. Sequential Organ Failure Assessment

Use the *worst* value (US units) for each physiological variable within the past 24 hours.

Respiration	
FiO_2	%
PaO_2	mmHg
Mechanical ventilation	No Yes
Coagulation	
Platelets	$x10^3/mm^3$
Liver	
Bilirubin	mg/dL
Neurological	
Glasgow coma score	
Cardiovascular	
MAP	mmHg
Vasopressors	No Yes
Renal	
Creatinine	mg/dL
Urine output	Greater than 500 mL/day
	Reset Calculate

SOFA model to predict 30-day ICU mortality. Publically available at
http://clincalc.com/IcuMortality/SOFA.aspx

Appendix E. Overall Predictive Performance of Prognostic Models in the Literature

Study	Prognostic Model (validation groups only)	AUC	Standard Error (SE)	95% Confidence Interval	Hosmer-Lemeshow goodness-of-fit *p* value
1.Benoit, et al (2003)	**APACHE II**	0.71	0.043	NP*	0.39
	SAPS II	0.77	0.043	NP	0.6
2. Berghmans, et al (2004)	**SAPS II**	0.72	0.045	NP	< 0.001
	APACHE II	0.65	0.047	NP	0.002
3. Can, et al (2008)	**APACHE II**	0.79	0.083	0.62 – 0.95	NP
	SAPS II	0.85	0.056	0.75 – 0.96	NP
4. Cardenas-Turanzas, et al (2012)	**SOFA** [1]	0.79	0.024	0.74 – 0.83	0.87
	SOFA [2]	0.79	0.063	0.63 – 0.94	0.01
5. Cornet, et al (2005)	**SOFA**	0.77	0.061	0.65 – 0.90	NP
	SAPS II	0.70	0.068	0.56 – 0.84	NP
6. Ertan, et al (2008)	**SAPS II**	0.83	0.064	NP	0.98
	APACHE II	0.78	0.070	NP	0.49
7. Fang, et al (2014)	**APACHE II** [3]	0.87	0.021	0.83 – 0.91	0.13
	APACHE II [4]	0.83	0.043	0.75 – 0.91	0.13

[1]Validation cohort, n = 540 medical patient group; [2] Validation cohort, n = 783 surgical patient group; [3] Validation cohort, n = 851 patients; [4] Validation cohort, n = 665 patients; *NP – Not provided

Study (continued…)	Prognostic Model (validation groups only)	AUC	Standard Error (SE)	95% Confidence Interval	Hosmer-Lemeshow goodness-of-fit *p* value
8. Greenberg, et al (2016)	**SOFA [5]**	0.68	0.038	0.61 – 0.76	0.25
	APACHE II [6]	0.65	0.039	0.58 – 0.73	0.31
9. Hampshire, et al (2009)	**APACHE II**	0.74	0.006	0.73 – 0.76	< 0.001
	SAPS II	0.74	0.006	0.73 – 0.75	< 0.001
10. Kopterides, et al (2011)	**APACHE II**	0.90	0.030	0.84 – 0.95	0.17
	SAPS II	0.83	0.040	0.75 – 0.89	0.22
	SOFA	0.87	0.030	0.80 – 0.93	0.14
11. Lamia, et al (2006)	**SAPS II [7]**	0.78	0.048	0.69 – 0.88	0.92
	SAPS II [8]	0.79	0.047	0.69 – 0.89	0.92
	SOFA[7]	0.78	0.048	0.69 – 0.88	0.32
	SOFA[8]	0.79	0.047	0.68 – 0.89	0.32
12. Liborio, et al (2011)	**APACHE II**	0.94	0.016	0.92 – 0.97	0.24
	SAPS II	0.87	0.023	0.83 – 0.91	0.24
	SOFA	0.91	0.020	0.88 – 0.94	0.24
13. Merz, et al (2008)	**SAPS II**	0.80	0.060	0.70 – 0.90	Og**
	SOFA	0.69	0.067	0.57 – 0.80	Og

[5] [6] Validation cohort, n = 196 patients; [7] Validation cohort, n = 92 patients; [8] Validation cohort, n = 81 excluding allogenic Hematopoietic Stem Cell Transplantation patients.

Study (continued…)	Prognostic Model (validation groups only)	AUC	Standard Error (SE)	95% Confidence Interval	Hosmer-Lemeshow goodness-of-fit *p* value
14. Namendys-Silva, et al (2010)	**APACHE II**	0.92	0.031	0.88 – 0.96	0.25
15. Namendys-Silva, et al (2012)	**APACHE II**	0.83	0.088	0.73 – 0.95	0.62
	APACHE II	0.87	0.031	0.88 – 0.96	0.25
16. Pohlen, et al (2016)	**SAPS II**	0.73	0.034	0.66 – 0.80	NP
	SOFA	0.78	0.032	0.71 – 0.86	NP
17. Schellongowski, et al (2004)	**APACHE II [9]**	0.78	0.036	0.71 – 0.83	0.06
	SAPS II [9]	0.83	0.027	0.77 – 0.88	0.07
18. Sculier, et at (2000)	**APACHE II**	0.60	0.038	NP	< 0.001
	SAPS II	0.67	0.037	NP	< 0.001
19. Soares, et al (2004)	**APACHE II [10]**	0.89	0.010	0.87 – 0.91	< 0.001
	APACHE II [11]	0.75	0.021	0.71 – 0.79	< 0.001
	SAPS II [10]	0.92	0.009	0.90 – 0.93	< 0.001
	SAPS II [11]	0.82	0.018	0.78 – 0.85	< 0.001
20. Soares, et al (2010)	**SAPS II [12]**	0.84	0.021	0.81 – 0.87	0.007
	SAPS II [13]	0.77	0.026	0.72 – 0.82	0.94

[9] Validation cohort, n = 242 medical cancer patients; [10] Validation cohort, n = 1257 including scheduled surgery patients; [11] Validation cohort, n = 542 medical and emergency surgical patients only.

Study (continued…)	Prognostic Model (validation groups only)	AUC	Standard Error (SE)	95% Confidence Interval	Hosmer-Lemeshow goodness-of-fit *p* value
21. Xing, et al (2015)	**APACHE II [14]**	0.86	0.036	0.804 – 0.923	0.900
	APACHE II [15]	0.87	0.069	0.774 – 0.958	0.594
	APACHE II [16]	0.83	0.045	0.757 – 0.911	0.594
22. Yan, et al (2012)	**APACHE II**	0.78	0.029	0.72 – 0.83	NP

[1]Validation cohort, n = 540 medical patient group; [2] Validation cohort, n = 783 surgical patient group; [3] Validation cohort, n = 851 patients; [4] Validation cohort, n = 665 patients; [5],[6] Validation cohort, n = 196 patients; [7] Validation cohort, n = 92 patients; [8] Validation cohort, n = 81 excluding allogenic Hematopoietic Stem Cell Transplantation patients; [9] Validation cohort, n = 242 medical cancer patients; [10] Validation cohort, n = 1257 including scheduled surgery patients; [11] Validation cohort, n = 542 medical and emergency surgical patients only; [12] Validation cohort, n = 717 patients; [13] Validation cohort, n = 336 without scheduled surgical patients; [14] Validation cohort n = 981; [15] Validation cohort, n = 70, non-scheduled surgery patients; [16] Validation cohort, n = 911, scheduled surgery patients; *NP – Not provided; ** Og = other goodness-of-fit test performed; *** NI = not indicated.

Appendix F. Characteristics of the Validated Studies Included in Meta-Regression

Study	Country	Location(s)	Study Period	Setting(s)	Sample Size (# of patients)	Cancer Type	Study Type	Type of prediction modeling	Statistical Software
Benoit, et al (2003)	Belgium	1 university hospital	Jan 1997 to June 2000	Adult MICU*	146	Solid & hematologic malignancy	Retrospective cohort study	EV†	SPSS 9.0
Berghmans, et al (2004)	Belgium	1 oncology specialty hospital	Jan 1999 to June 2000	Adult** MICU-O	247	Solid & hematologic malignancy	Prospective cohort study	EV	Not indicated
Can, et al (2008)	Turkey	1 tertiary community hospital	Sept 2003 to March 2006	Not indicated	224	Colorectal cancer (surgical resection)	Prospective cohort study	EV	SPSS 11.0
Cardenas-Turanzas, et al (2012)	USA	1 university-affiliated, oncology specialty hospital	Jan 2006 to Dec 2008	Adult*** MSICU	6645	Hematologic and solid malignancy	Cross-Validation, Retrospective cohort study	PM†ŧ (n = 2069, medical) + (n = 3253, surgical) with EV (n = 540) + (n = 783, surgical)	PASW 17.0
Cornet, et al (2005)	Netherlands	1 university hospital	Nov 1995 to Dec 2002	Adult MICU	58	Acute Myeloid Leukemia and non-Hodgkin lymphoma	Retrospective cohort study with prospective follow-up	EV	Not indicated
Ertan, et al (2008)	Turkey	1 university hospital	Jan 1998 to July 2004	Not indicated	102	Colorectal cancer	Retrospective cohort study	EV	Not indicated
Fang, et al (2014)	China	1 tertiary community hospital	1991 – 2011	Adult*† ICU-NS	851	Gastric cancer (surgical resection)	Retrospective cohort study	EV	STATA 11.0
Greenberg, et al (2016)	USA	1 university-affiliated hospital	Sept 2009 to Sept 2014	Adult MICU	246	Hematologic malignancy	Retrospective cohort study	PM (n = 50) with EV (n = 196)	STATA 13.1
Hampshire, et al (2009)	United Kingdom	178 hospitals	Dec 1995 to March	Adult MSICU	7,689	Solid & hematologic	Retrospective cohort study	EV	STATA 9.2

			2007			malignancy			
Kopterides, et al (2011)	Greece	1 university hospital & 1 tertiary hospital	Jan 2005 to Dec 2007	Adult MSICU	126	Solid & hematologic malignancy	Prospective observational study	EV	SPSS 10.0 & MedCalc 16.6
Lamia, et al (2006)	France	1 university hospital	Jan 2000 to July 2003	Adult MICU	92	Hematologic malignancy	Retrospective cohort study	EV	STATA 8.0
Liborio, et al (2011)	Brazil	1 oncology specialty hospital	May 2006 to June 2008	Adult**† MSICU-O	288	Solid & hematologic malignancy	Prospective observational study	EV	SPSS 17.0
Merz, et al (2008)	Switzerland	1 university hospital	July 2001 to July 2005	Adult MSICU	101	Hematologic malignancy	Retrospective cohort study	EV	SPSS 13.0
Namendys-Silva, et al (2010)	Mexico	1 oncology specialty hospital	Jan 2007 to Oct 2007	Adult MSICU-O	117	Solid malignancy	Prospective observational study	EV	SPSS 15.0
Namendys-Silva, et al (2012)	Mexico	1 oncology specialty hospital	Jan 2007 to Oct 2007	Adult MSICU-O	52	Gynecological cancer	Prospective observational study	EV	SPSS 15.0
Pohlen, et al (2016)	Germany	3 university-affiliated, hospitals	Nov 2004 to Sept 2011	Adult ICU-NS	451	Acute Myeloid Leukemia	Cross-Validation, Retrospective cohort study	PM (n = 187) with EV (n = 264)	SPSS 22.0
Schellongowski et al (2004)	Austria	1 university oncology specialty hospital	March 1998 and July 2002	Adult MSICU	242	Solid & hematologic malignancy	Prospective cohort study	EV	SAS
Sculier, et at (2000)	Belgium	1 oncology specialty hospital	Oct 1992 to Aug 1995	Adult MICU-O	261	Solid & hematologic malignancy	Prospective cohort study	EV	Not indicated
Soares, et al (2004)	Brazil	1 oncology specialty hospital	May 2000 to July 2003	Adult MSICU-O	1972	Solid & hematologic malignancy	Prospective observational study	EV	SPSS 10.0

Study	Country	Location(s)	Study Period	Setting(s)	Sample Size (# of patients)	Cancer Type	Study Type	Type of prediction modeling	Statistical Software
Soares, et al (2010)	Brazil	28 Hospitals	Aug 2007 to Sept 30, 2007	Adult MSICU (n = 23) & Adult MSICU-O (n = 5)	717	Solid & hematologic malignancy	Prospective multi-center cohort study	EV	Not indicated
Xing, et al (2015)	China	1 university-affiliated, oncology specialty hospital	Oct 2008 to Sept 2010	Adult MSICU	981	Solid malignancy	Retrospective cohort study	EV	SPSS 16.0
Yan, et al (2012)	China	2 university-affiliated, hospitals	Jan 2005 to Dec 2009	Adult ICU-NS	1695	Colorectal cancer (surgical resection)	Retrospective Cohort study	EV	SPSS 19.0

*Adult MICU = Adult Medical Intensive Care Unit; **Adult MICU-O = Adult Oncology Medical Intensive Care Unit; ***Adult MSICU = Adult Medical and Surgical Intensive Care Unit; *ǂ Adult ICU-NS = Adult Intensive Care Unit – Not Specified; ** ǂAdult MSICU-O = Adult Oncology Medical and Surgical Intensive Care Unit; ǂ External validation = to assess and compare the predictive performance of an existing prediction model using new participant data; ǂǂ Prediction model = the development of the model is followed by quantifying the model's predictive performance in participant data external to the development dataset.

Appendix G. Curriculum Vitae

Sheila Donnell, MS, APRN, WHCNS, AOCNS, OCN

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Cell : (817) 372 - 7489

OBJECTIVE

Seeking an opportunity to collaborate and contribute to achieving optimal clinical outcomes by applying translational research, education , and scholarship to inter-professional collaborations among nursing, medicine, and allied health professionals.

PROFESSIONAL EDUCATION & ACADEMIC TRAINING

University of Texas at Tyler, Tyler, TX – PhD(c), Nursing pending completion of dissertation
Dissertation topic: Meta-Regression: Prognostic Models' as Objective Predictors of Mortality among ICU Cancer Patients

Texas Woman's University, Denton, TX – M.S., Health Studies May, 2014
Topics of interest: health education-focused program development, coordination, and evaluation; health education-centered inter-professional collaboration between nursing, medicine & allied health.

Texas Woman's University, Dallas, TX – M.S., Nursing, Clinical Nurse Specialist December, 2002
Thesis: Normal Emotional Changes during Pregnancy vs. Antepartum Depression

Prairie View A&M University, Prairie View, TX – B.S.N. in Nursing December, 1993

CERTIFICATION - LICENSURE

RN Licensure- Board of Nurse Examiners for the state of Texas – June, 2018
Women's Health Clinical Nurse Specialist, certification (WHCNS) - Board of Nurse Examiners for the state of Texas with prescriptive authorization (Rx Auth.) - June, 2018
Advanced Oncology Clinical Nurse Specialist, certified (AOCNS) - December, 2020
Oncology Certified Nurse (OCN) - December, 2019
Chemotherapy provider, certified – May, 2018
Critical Care Support, certified (FCCS) - May, 2017

PROFESSIONAL AFFILIATIONS

National Association of Clinical Nurse Specialists (NACNS)
North Texas Clinical Nurse Specialists (NTCNS)
Oncology Nursing Society (ONS)
Phi Kappa Phi (PKP)
Sigma Theta Tau International, Honor Society of Nursing (STTI)

ABSTRACTS & NATIONAL PRESENTATIONS

- Donnell S, Everidge, T, Brown, A, Tripathy, D. Patterns of breast cancer detection and diagnosis in a community hospital. Submitted for 31st Annual San Antonio Breast Cancer Symposium, December 2008.

- Donnell S, Leitch AM, D. Rice D, E. Gray E, McKindles D, Aravind R, Warungi M, Youssefi F, Osborne C, Tripathy D. Navigator program for breast cancer trial recruitment and enrollment at a county hospital. Journal of Clinical Oncology 23(16S):28S (Abstract 598), May 2005.

- Donnell SK, Leitch AM, Gray E, Aravind R, McKindles D, Tripathy D. Breast cancer navigator program: clinical trial access, recruitment and enrollment at a large county hospital. Breast Cancer Research & Treatment 94(Suppl1):S102 (Abstract 2055), December 2005.

RESEARCH **E**XPERIENCE & **C**LINICAL **T**RIALS **N**AVIGATION

A Cluster-Randomized, Controlled, Multi-Center Study of How Oncologists Present Chemotherapy and Hormone Therapy Benefits and Risks (ASSERT).
Breast Cancer Repository for the Prospective Acquisition of Blood and Tissue Samples.

Contrast-enhanced Breast MRI and Correlative Science Studies to Characterize Tumor Response in Patients undergoing Neo-adjuvant Treatment for Locally Advanced Breast Cancer [CALGB 140007/ACRIN 6657].

Intraoperative Lymphatic Mapping for Stage I and II Breast Cancer Using Technetium Sulfur Colloid and Isosulfan Blue.

Investigating Mechanisms to Explain Age Associated Differences in Quality of Life Among Breast Cancer Patients.
Menstrual Cycle Maintenance and Quality of Life: A Prospective Study.

Phase III Trial of Intraveneous Zoledronic Acid in the Prevention of Bone Loss in Localized Breast Cancer Patients with Chemotherapy-induced Ovarian Failure.

Prognostic Radiology: Prediction and Early Detection of Treatment Efficacy for Therapeutic Optimization - Breast Cancer.

Ramdomized, Two Arm, Placebo-controlled Double Dummy Study to Compare the Efficacy of Intravenous Loading Doses Followed by Maintenance Treatment with Oral Ibandronic Acid vs. Zoledronic Acid in Patients with Skeletal Metastases Experiencing Moderate to Severe Pain.

AWARDS/**S**CHOLARSHIPS

- 2012 Texas Health Harris Methodist Auxiliary Scholarship for commitment and dedication to a career in the field of medicine; $3,500.