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Characterization of medication regimen complexity, pharmacist interventions, and patient outcomes in critically ill patients

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A thesis submitted to the Faculty of the
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Abstract

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Despite the established role of the critical care pharmacist (CCP) on the intensive care unit (ICU) interprofessional team and their proven benefit to critically ill adults, CCP workloads are not optimized in the ICU. Lack of optimization has important ramifications for patients, CCPs, and institutions. Challenges to optimizing CCP staffing models include lack of validated predictive metrics to define CCP resource needs across different ICU and hospital types. Medication regimen complexity (as measured by the MRC-ICU Scoring Tool) has been proposed as a potential metric to optimize CCP workload. This algorithmic tool is a 39-line item medication weighted scoring system based on the patient's current medications. The purpose of this multi-center, observational cohort study was to test the hypothesis that medication regimen complexity is related to both patient outcomes and pharmacist activity. CCP interventions on the medication regimens of critically ill patients over a four week period were captured. MRC-ICU, patient outcomes (i.e., mortality and length of stay (LOS)), and CCP interventions (quantity and type) and were recorded retrospectively from review of electronic medical records. The co-primary outcomes included the relationship of MRC-ICU to mortality and number of CCP interventions. Multivariable analysis was performed to identify factors associated with patient outcomes and CCP interventions. A total of 1,216 patients at 28 centers were included. The most common practice setting was the medical ICU (48.8%) followed by neurosciences (18.5%) and mixed ICU (10.7%). The mean MRC-ICU score was 10.4 (± 6.3). Following analysis of variance (ANOVA), MRC-ICU was significantly associated with mortality ($p < 0.01$), ICU LOS ($p < 0.01$), and total pharmacist interventions ($p < 0.01$). When comparing the first vs. fourth MRC-ICU quartiles, the incidence of mortality doubled (14.1% vs. 30.5%, $p < 0.01$), ICU LOS tripled (8.0 v. 24.1 days, $p < 0.001$), and number of interventions increased (7.6 v. 9.8 interventions, $p < 0.01$). Multiple linear regression demonstrated that for every one point increase in MRC-ICU score, pharmacy intervention quantity increased by 0.11 interventions (95% CI 0.06 – 0.15, $p < 0.01$) and a composite score of intervention quality increased by 0.23 (95% CI 0.05 – 0.41, $p = 0.03$). Further, a multiple linear regression model demonstrated that ICU LOS independently increased by 0.75 days (95% CI 0.32 – 1.19, $p<0.01$) for each point increase in the MRC-ICU score independent of potential confounding patient and organizational factors. In multivariate regression analysis, pharmacist-to-patient ratio was significantly associated with total number of interventions (ß coefficient -0.02, 95% CI -0.04 – -0.01, $p = 0.03$) showing that increased patient load was associated with reduced overall interventions. In summary, quantification of medication regimen complexity in critically ill adults has shown promise by its relationship to important process and outcome measures, and future research should evaluate use of objective metrics like medication regimen complexity to inform CCP staffing models and how they affect patient outcomes.

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INTRODUCTION

Critical care pharmacists (CCP) improve patient outcomes and reduce healthcare costs but remain an underused healthcare resource in the intensive care unit (ICU).(1-9) These highly trained professionals generate benefit through direct patient care activities, participation on the ICU interprofessional team, and leadership in the development and implementation of quality improvement initiatives.(1-8, 10-17)

The breadth of these beneficial activities has been supported by the 2020 position statement from American Society of Health-Systems Pharmacists (ASHP)/American College of Clinical Pharmacy (ACCP)/Society of Critical Care Medicine (SCCM) declaring that CCP are essential members of the healthcare team for delivery of patient-centered care in the intensive care unit (ICU).(18) However, this position paper provides little guidance on approaches to justify critical care pharmacist positions or how CCP positions can be structured to achieve the standards outlined.(18, 19) Indeed, while establishing appropriate CCP-to-patient ratios is considered "foundational," the authors state "limited data are available to guide optimal ratios" and "determinations regarding coverage and service design should be based on patient acuity and complexity and the scope of pharmacist services to ensure that critical care pharmacists are allocated time to perform the full range of patient care and other services associated with improved outcomes."

In the U.S., there are only 2,400 board certified critical care pharmacists available to provide care to 100,000 ICU beds filled with 5 million patients each year; a substantial shortage of qualified CCP exist to provide an optimal level of pharmacotherapy care at the recommended pharmacist-to-patient ratio of 1:15.(20-24) This challenge is faced across the discipline of critical care medicine where a SCCM taskforce published a report stating unsustainable staffing gaps for

physicians, advanced practice providers, and nurses and considerable risk for clinician burnout.(25, 26)

Barriers to defining the optimal pharmacy practice model and the optimal pharmacist-to-ICU patient staffing ratio

Globally, the relationships that define the optimal pharmacist-to-patient ratio, the quality of CCP care, and the resulting ICU patient-related outcomes remains poorly characterized.(28) Among ICUs in the United Kingdom, research focused on pharmacist staffing resources, time spent by pharmacists in the ICU conducting direct patient care activities, and the quality and impact of CCP interventions achieved, support the relationship that pharmacist-to-patient ratio and quality of care. Further, evaluation of how other healthcare provider-to-patient ratios affects the quality of patient care indicates that an overburdened workforce results in reduced quality of care.(30-32)

Application of this research to U.S. CCPs, where pharmacist practice models are quite different, healthcare reimbursement is different, and CCP training is more advanced, is limited.(33-36) The optimal pharmacist-to-patient ratio has been projected to range between 1:8 and 1:30.(20-24) Most (75%) CCPs place it around 1:15, which is despite 27% of CCP reporting working at a ratio of 1 CCP to 18 ICU patients and another 25% reported working at a ratio of 1 CCP to 30 or more ICU patients.(27) However, these values are based on self-report and lack consideration of ICU demographics and expected CCP responsibilities.

Indeed, while many before-after studies have clearly shown the addition of a CCP to the ICU interprofessional team improves patient outcomes, the intensity by which CCP services should be delivered to optimize patient care outcomes remains unclear. If a CCP has fewer ICU patients to care for, does their effectiveness improve? If CCP services are also delivered on

evenings and/or weekends, are ICU patient outcomes further optimized? What factors most influence the optimal pharmacist-to-patient ratio that should be delivered (e.g., severity of illness, number and/or type of medications)? Are there additional CCP responsibilities with equally positive effects on patient outcomes that might influence this staffing ratio such as teaching, quality improvement, or medication order validation? Globally, no study has formally evaluated how the pharmacist-to-patient ratios affects number or quality of medication interventions, patient outcomes, healthcare costs, or pharmacist wellbeing.

Key knowledge gaps to optimizing CCP staff models include unknown mechanisms of how CCP improve patient outcomes, lack of standard methodology for characterizing CCP productivity, and lack of validated predictive metrics for CCP resources. Strategies to resolve these issues include development of a CCP-specific metric that quantifies activities and allows for comparisons among practice models. Barriers and strategies are presented in **Table 1.** (6, 28, 37-62)

These knowledge gaps prevent pharmacy administrators from being able to individualize CCP scheduling to a specific ICU patient ratio goal that will maximize return on investment (ROI). Failure to fully optimize the efficiency of this expensive resource may hinder CCP service expansion and have the unintended consequence of dictating CCP practice models by available resources as opposed to patient outcomes guiding the need for new resource allocation.(18) This approach to CCP modelling precludes allowing desired ICU clinical outcomes to drive, refine, and optimize the CCP model best suited to a particular ICU. As knowledge of pharmacist-to-patient ratio individualization continues to evolve (1-8, 27) and CCP ratios improve, reduced medication-associated harm, healthcare waste, and critical care pharmacist burnout should ensue.(27-29)

BACKGROUND

Existing tools to describe pharmacist workload

A reliable metric to define and incorporate the key domains and outcomes of CCP performance (e.g., the institutional resources to hire and support CCP and the influence of these pharmacists on patient outcome and medication-related healthcare costs) has a strong potential to influence the development of robust CCP practice models. Several tools and models have been developed including the pharmacist Census, patient Acuity, Teaching services, medication Cost, and use of High priority medications (pCATCH) score, pharmacist intensity score (PIS), and medication regimen complexity index (MRCI). However, these tools are significantly limited in their ability to answer questions relevant to CCP due to single-center validation and lack of ICU or clinical pharmacy specific orientation. Strengths and limitations of these tools are summarized in **Table 2**.

MRC-ICU Scoring Tool

The MRC-ICU Scoring Tool is the first validated tool developed to provide an objective measurement of medication regimen complexity for critically ill patients.(63) This instrument is comprised of 39 items consisting of both high-risk medications and devices (**Appendix 1**). Items are individually weighted based on complexity and degree of pharmacist intervention/expertise required for review and management. The MRC-ICU Scoring Tool is designed to connect the components of the optimal practice model (i.e., patient outcomes, healthcare costs, pharmacist welfare, and pharmacist resources). Ultimately, the MRC-ICU may provide real-time guidance to optimize pharmacist-to-patient ratios in the critical care setting and direct clinician attention to patients at particularly high risk for poor outcomes.

Initial development and validation: The MRC-ICU was developed and validated by adapting the methods used for the Medication Regimen Complexity Index (MRCI).(51-52, 64) After scoring 15 regimens, the tool was discussed among three investigators to identify areas of discrepancy and to clarify ease of use. Then, one investigator scored 130 medical ICU (MICU) patient records at 24 hours after admission. Exclusion criteria consisted of length of stay (LOS) of less than 24 hours in the MICU, active transfer, or hospice orders at 24 hours. Construct, convergent, discriminant, and internal validity were confirmed. Further, interrater reliability was established through three investigators scoring the same 15 regimens and then through two independent scorers evaluating test-retest reliability by scoring 25 regimens at an interval of 2 weeks.

Further analysis of the MRC-ICU score revealed a significant correlation with patient acuity ($r = 0.4084$, $p < 0.0001$) and patient outcomes including LOS ($r = 0.2097$, $p = 0.0166$) and mortality (living vs. not living: 13.7% vs 16.7%, $p = 0.0193$) (64).

External validation by institution and ICU: Subsequently, a prospective study of 230 patients in both a MICU and a surgical ICU (SICU) was conducted at an academic medical center and a community teaching hospital.(65) Convergent validity was demonstrated by correlating the MRC-ICU score with total medications among the MICU, SICU, and combined critical care populations, and appropriate correlation was observed (all $p < 0.001$). Discriminant validity was shown by a lack of correlation of these same groups with age, gender, and weight (all $p > 0.1$). Correlation coefficients from each ICU population were similar despite significant differences in practice sites, suggesting external validity.(66)

MRC-ICU and pharmacist related outcomes: To objectively quantify pharmacist activity, a study was conducted to determine if the MRC-ICU (and mMRC-ICU) score correlated with

pharmacists interventions and potential drug-drug interactions (DDIs).(66-67) In this dual center study of mixed ICU populations, critical care pharmacists prospectively recorded all interventions made over the course of the ICU admission. The MRC-ICU was scored at 24 hours, 48 hours, and ICU discharge, and DDIs were recorded at the same time points. MRC-ICU at 24 hours correlated with pharmacist interventions at 24 hours and cumulative interventions at discharge ($r=0.356$, $p<0.001$; $r=0.439$, $p<0.001$) while scores at 48 hours and discharge did not have the same predictive value. MRC-ICU at 24 and 48 hours also predicted patient acuity and LOS (all $p < 0.005$) confirming findings of the original study. DDIs were shown to be correlated to both the MRC-ICU score ($r=0.4$, $p < 0.001$) and the mMRC-ICU score ($r=0.479$, $p < 0.001$) at 24 hours. Correlation with potential DDIs was an expected finding as DDIs are known to increase with total number of medications; this serves as another validity confirmation, but also suggests a potential clinical use to identify high-risk patients.(68, 69)

MRC-ICU as a dynamic index: Medication regimen complexity has been shown to be a dynamic measurement that changes over the course of a patient's admission. The MRC-ICU score was evaluated in 130 patient regimens at 24 hours, 48 hours, and ICU discharge. The MRC-ICU at 24 hours was significantly higher than the score at 48 hours (14.7 vs. 8.4, $p<0.0001$) and discharge (17.4 vs. 6.3, $p<0.0001$). The MRC-ICU score at ICU discharge was lower than at 48 hours, but this difference was not statistically significant (8.4 vs. 6.3, $p = 0.097$). Interestingly, the MRC-ICU score at 48 hours and discharge did not correlate to pharmacist interventions in the initial pilot study, though a possibility exists that this study was not appropriately powered to observe this relationship.(67) Further evaluation of medication regimen complexity as a dynamic index predicting pharmacist resources is warranted.

Medication regimen complexity as predictor for ICU patient status: For a construct such as medication regimen complexity to be effective, evaluation of the relationship with 'real-time' outcomes such as fluid overload and delirium is needed. In a multi-center, retrospective study of 125 medical and surgical patients, for each point increase in MRC-ICU, a 13% increase in the likelihood of fluid overload was observed (OR 1.128, 95% CI 1.028 – 1.238, p = 0.011) following logistic regression controlling for gender, age, and weight.(37, 70, 71)

Figure 1 describes the MRC-ICU research pathway to date. While this metric has shown initial potential to objectively describe medication regimen complexity, lack of large, multi-center, multi-ICU evaluation limits external validity. The purpose of this study was to provide initial characterization of the MRC-ICU in a large, diverse population of critically ill patients and to explore its predictive ability for patient-centered outcomes (i.e., mortality, ICU LOS) and pharmacist activity (i.e., CPP intervention quantity and quality).

METHODS

The rationale for this study was to relate medication regimen complexity as measured by MRC-ICU with patient-centered outcomes and pharmacist activity. The goal of this study was to evaluate the MRC-ICU's relationship to patient outcomes (i.e., mortality, LOS) and pharmacist activity (i.e., quantity and quality of pharmacist interventions) in diverse critically ill populations.

Aim 1: Evaluate the relationship between MRC-ICU and patient outcomes

Hypothesis 1a: Increasing MRC-ICU independently increases odds of hospital mortality

Hypothesis 1b: Increasing MRC-ICU independently increases ICU LOS

Aim 2: Evaluate the relationship between MRC-ICU and pharmacist interventions

Hypothesis 2a: Increasing MRC-ICU independently increases the quantity of pharmacist interventions

Hypothesis 2b: Increasing MRC-ICU independently increases the quality of pharmacist interventions

Study Design

This study was a prospective, multi-center, observational study that captured CCP interventions over 4 weeks. Retrospective chart review was used to capture patient outcomes and MRC-ICU.

Study Population

Inclusion criteria were adult patients (>18 years old) admitted to an ICU setting that were cared for by participating pharmacists during the study period. Exclusion criteria included an ICU stay of less than 24 hours and presence of hospice orders.

Variables

Data including institution characteristics, patient outcomes, components of the MRC-ICU score, pharmacist-to-patient ratio, and pharmacist interventions were collected. Institution characteristics included institution type, ICU type, and geographic region. Patient outcomes included mortality and ICU LOS. Quantity of interventions was defined as the total number of interventions recorded per patient for their ICU stay. These interventions were ranked as low, medium, and high quality interventions by three investigators through independent categorization **(Table 3)**.

Statistical Analysis

Descriptive statistics were performed including summary statistics for all outcomes, predictor, and co-variate variables. This sample was a convenience sample with sample size determined by number of participants and their census during the data collection period.

Two exposure variables were evaluated: medication regimen complexity and pharmacist-to-patient ratio. Four outcome variables were evaluated: mortality, LOS, quantity of pharmacist interventions, and quality of pharmacist interventions.

A histogram of MRC-ICU distribution was plotted, and four quartiles were developed. Univariate analysis of variance (ANOVA) was evaluated for MRC-ICU quartiles and their relationship to mortality, ICU LOS, quantity of interventions, and quality of interventions.

Multivariate regression models were developed to evaluate the relationship of MRC-ICU and pharmacist-to-patient ratio in relation to mortality, ICU LOS, quantity of interventions, and quality of interventions. Specifically, a multivariate logistic regression model was used to describe the odds of hospital mortality based on medication regimen complexity. Multivariate

linear regression models were used to describe increasing LOS, CPP intervention quantity, and CPP intervention complexity given medication regimen complexity. Each model included co-variates *a priori* considered potentially confounding the relationship between independent and dependent variables: institution type, ICU type, and geographic region. Linear regression model results are reported as coefficient estimates (e.g. change in LOS) with 95% confidence intervals and logistic regression model results are reported as odds ratios (OR) with 95% confidence intervals.

Statistical significance was set at $p < 0.05$ for two-tailed tests. All analysis was completed in R (ver. 3.6.1). Results are presented as mean (standard deviation) or total (percent) unless otherwise noted. Institutional review board approval was obtained through Augusta University Medical Center.

RESULTS

This study included a total of 1,216 patients from 28 institutions. Most patients were cared for at academic medical centers (991, 88.3%) with the largest number admitted to a medical ICU (600, 48.8%). The mean (SD) MRC-ICU score was 10.4 (6.3). The pharmacist-to-patient ratio was 22.8 (18.3), and CCPs completed 8.4 (4.7) interventions per patient. Demographic characteristics and a summary of patient outcomes are summarized in **Table 4**.

Cardiovascular surgery had the highest mean MRC-ICU of 15.4 (7.7), and medical ICU, which had the largest number of patients, had a mean score of 8.4 (5.3). MRC-ICU percentiles were 5 (25^{th} percentile), 9 (50^{th} percentile), and 15 (75^{th} percentile). Significant differences among quartiles were present for patient characteristics including presence of continuous renal replacement therapy and mechanical ventilation, institution type, and region of the United States (see **Table 5**).

Aim 1: Evaluate the relationship between MRC-ICU and patient outcomes

Increasing MRC-ICU quartile was significantly associated with increased mortality. The incidence of mortality doubled from the lowest to highest quartile (14.1 vs. 30.5, $p < 0.01$) (see **Table 5**). While MRC-ICU score was associated with mortality in univariate analysis (OR 1.08, 95% CI 1.05 – 1.10, $p < 0.01$), after adjusting covariates in the multivariate regression model, rising MRC-ICU scores were not independently associated with hospital mortality (OR 1.02, 95% CI 0.98 – 1.06, $p = 0.31$). **Table 6** summarizes factors associated with mortality.

LOS was significantly associated with MRC-ICU quartile, with ICU LOS tripling from the lowest to highest quartile (8.0 vs. 24.1, $p < 0.01$) (see **Table 5**). After adjusting for potential confounding factors in the multivariate linear regression model, each point increase in the MRC-ICU was independently associated with a 0.75 day longer ICU LOS (95% confidence interval

(CI) 0.32 – 1.19 days, $p < 0.01$). **Table 7** summarizes factors associated with LOS. Notably, pharmacist-to-patient ratio was not statistically significantly associated with either mortality or LOS.

Aim 2: Evaluate the relationship between MRC-ICU and pharmacist interventions

The quantity of pharmacist interventions was significantly associated with MRC-ICU quartile and increased with each higher quartile (lowest to highest quartile comparison: 7.6 v. 9.8, $p < 0.01$ (see **Table 5**). After adjusting for potentially confounding factors in the multivariate linear regression model, each point increase in the MRC-ICU was independently associated with a 0.11 greater total number of interventions per patient (95% CI 0.06 – 0.15, $p < 0.01$). Interestingly, the regression model also identified a relationship between pharmacist-to-patient ratio and the number of interventions per patient with each increase additional patient per pharmacist independently decreasing the quantity of interventions per patient by 0.02 (95% CI -0.04 – -0.01, $p = 0.03$). **Table 8** summarizes other factors associated with the quantity of interventions.

Quality of interventions was assessed through the development of a composite score, which weighted both the quality and quantity of interventions. No significant difference was observed by MRC-ICU quartile (see **Table 5**). After adjusting for potentially confounding factors in the multivariable linear regression model, each point increase in the MRC-ICU was independently associated with a 0.23 point increase in intervention quality score (95% CI 0.05 – 0.41, $p = 0.03$). Pharmacist-to-patient ratio was not associated with quality of interventions. **Table 9** summarizes factors associated with quality of interventions.

DISCUSSION

In the first large-scale, prospective, multi-center analysis, MRC-ICU demonstrated relationship to both patient outcomes and pharmacist activity. These results support MRC-ICU as an objectively calculated, validated means to calculate the metric of medication regimen complexity across a diverse patient population of critically ill patients. Further, this study demonstrates for the first time that increased pharmacist-to-patient ratio is associated with lower intervention quantity (and thus potentially how high CPP workload adversely affects patient care provided).

A relationship between medication regimen complexity and mortality was observed, which builds upon several smaller studies.(12-14) This relationship was not observed in multi-variate regression analysis adjusting for institutional demographics, but this study was unable to adjust for the potential interacting relationship between medication regimen complexity and patient acuity. The combination of medication regimen complexity and patient acuity using machine learning methodology has been shown to be a more useful mortality predictor than either factor alone and inclusion of this co-variate is warranted in future investigations.(13)

LOS remained significantly associated with medication regimen complexity through both univariate and multivariate analysis, in line with previous studies.(6, 7, 15, 16) Increased quantity of interventions was also related to decreases in LOS. Although these interpretations are limited by lack of acuity data, these results represent an important signal. While well known that number of medications increases risks of adverse drug events (ADEs) *and* that many medications used in the ICU setting pose a high risk for ADEs, formally linking medication regimen complexity to both LOS and CCP activity presents a unique finding.(17-19) Particularly salient for CCPs is that pharmacologic knowledge is known to reduce ADEs, and CCPs are also known

to reduce ADEs, thus allowing for the hypothesis that having a healthcare professional with high amounts of pharmacologic knowledge may be the causative factor for reducing ADEs.(20, 21)

Further, pharmacist-to-patient ratio was included in the multivariate models of medication regimen complexity. Little is known about how the workload of a CCP affects patient outcomes or the quality of their clinical interventions. The observation that as pharmacist-to-patient ratio increased, the number of interventions decreased is a novel finding that warrants further investigation in appropriately designed, prospective studies.

Application and future directions for metrics focused on optimized CCP services

ICU patients are a highly heterogenous and dynamic patient population. As such, both medication regimen complexity and CCP requirement are likely to change with patient status. Thus, information technology (IT) tools to manage the huge array of medications and patient characteristics may be needed to calculate an accurate pharmacist-to-patient ratio to make real-time, precision-oriented recommendations.(20, 24) Ideally, this health IT tool will aid CCPs to quickly synthesize highly complex, dynamic data to visualize clinically useful predictions. The gaps in knowledge in the field of CCP practice can be summarized as uncharacterized relationships between (1) current patient status and CCP interventions (2) quantity and type of CCP interventions and patient outcomes; (3) pharmacist-to-patient ratio and CCP interventions; and (4) pharmacist-to-patient ratio and patient outcomes. Most notably, no validated metrics exist to establish predictive models upon which to delineate the interactions of these factors. The purpose of this investigation was to further characterize a validated metric to predict the number of CCP(s) needed to optimally care for an ICU population. This investigation will aid determination of the optimal pharmacist-to-patient ratio needed to optimize outcomes.

Potential roles for a metric like MRC-ICU include providing resource predictions from a hospital administrative perspective for CCP position justification, real-time guidance to establish optimal pharmacist-to-patient ratios, and clinician-oriented information for prioritization of those critically ill adults who are at greatest risk for unfavorable medication-related outcomes (e.g., fluid overload). Use of validated metrics beyond cost avoidance has important ramifications for future position justification (see **Appendix 2**). Ideally, this study, by applying this metric in a wide variety of institution types and ICU settings without losing translatability, can establish a common language to investigate and corroborate the idea that best-pharmacy practice models can be proactively instituted.

A potential construct for applying such a metric may be where resources are objectively predicted by an algorithm and patient outcomes evaluated as a result of this staffing model, allowing for future site-specific modifications. In such a construct, patient specific data and a pharmacy-based metric would be fed into a predictive model that provides both predictions for patient outcomes (e.g., mortality, fluid overload) and pharmacist resources per patient (e.g., number of interventions, time per intervention, etc.). At this juncture, institution specific needs (e.g., unit census, non-patient care responsibilities of the pharmacist) would be incorporated to identify a reasonable pharmacist-to-patient ratio and associated staffing model. This staffing model would then be evaluated based on actual patient outcomes and pharmacist activities against the tool's original predictions to allow for further optimization.

A proof-of-concept model using machine learning methods to validate the MRC-ICU score was developed and despite a small data set, the results suggest prediction of patient outcomes can be improved with inclusion of medication regimen complexity data and the MRC-ICU score over the traditional predictor of APACHE III.(72) Our research suggests that a

machine learning-validated MRC-ICU Scoring Tool can predict CCP interventions that improve patient outcomes based on current patient status (e.g., a patient at high risk of ADE would trigger an alert for CCP intervention that then prevents this potential ADE). By identifying the quantity and type of CCP interventions necessary based on the patient's real-time status, the MRC-ICU Scoring Tool may identify the currently unknown optimal pharmacist-to-patient ratio (see **Figure 2**).

Strengths and limitations

Specific strengths of this study included that it is the first and largest study to date to evaluate medication regimen complexity and pharmacist interventions. This study also represents the first time that pharmacist-to-patient has been explored in its relationship to either patient outcomes or pharmacist activity. Further, its prospective, multi-center, multi-ICU design supports external validity.

Several limitations are present. The study population consisted of patients care for by CCP members of Society of Critical Care Medicine that chose to participate in a relatively extensive research project and who happened to largely work at academic medical centers. Further, there was relative under-representation of certain ICU types (e.g., surgical, burn). Taken together, these may limit external validity. Second, all CCP interventions were based on voluntary self-reporting, which may introduce bias that includes both under-reporting or over-reporting. As such, this study utilized convenience based sampling with reporting happening when pharmacists were on-service/available during a 4-week period, which potentially limits the ability to make determinations regarding associations between ratios and outcomes. Third, objective illness severity indicators were not collected, allowing for the possibility that the most

critical patients had the most interventions but were still most likely to have worse outcomes regardless of clinician intervention.

In summary, although these limitations preclude definitive conclusions about the relationship of pharmacist-to-patient ratio and outcomes, the results add important insights and informs further investigations that likely need to include more granular information regarding patient acuity and specified staffing information.

CONCLUSION

ICU workload for pharmacists has not been optimized and exposes critically ill patients to worse outcomes and increased healthcare costs. In the first large, multi-center, multi-ICU study of the MRC-ICU, medication regimen complexity demonstrated key relationships to patient outcomes and pharmacist activity. Use of a quantifiable and externally valid metric that allows for cross-institution and cross-patient population evaluation of patient outcomes, healthcare costs, pharmacist welfare, and pharmacist resources has strong potential for improving patient outcomes through optimization of CCP resources.

Table 1. Knowledge Gaps to CCP Staffing Model Optimization and Strategies to Resolve

Knowledge Area	Gap Description	Resolution Strategies
1. CCP activity and patient outcome Mechanism	• Unknown relationship between CCP activities and ICU patient outcomes. • Most studies focus on process measures (e.g., intervention quantity vs. impact on patient outcome)	• Increased research linking CCP activities to process and outcome measures
2. Daily CCP value assessment	• No standardized or efficient method. Cannot reliably measure the amount of CCP time spent on an intervention, how many interventions a particular ICU patient will require, or whether an intervention with a *potential* clinical benefit will actually contribute to beneficial outcomes like reduced ICU LOS • Productivity tracking is dependent on the CCP efforts to individually record and appropriately classify each intervention, introducing bias	• Internal and external benchmarking could be extremely useful in CCP justification • Investigate the relationship of CCP responsibilities to quality of interventions to optimize CCP responsibilities during their shift
3. CCP value assessment	• Intervention tracking captures many direct patient care activities but does not capture other indirect activities (e.g., protocols) that prevent the need for direct 'interventions' • Difference between cost avoidance and savings limits value assessments	• Real-time documentation of CCP interventions that includes both direct and indirect interventions is needed
4. ICU pharmacy practice models description (and comparisons)	• Comparisons of ICU staffing among institutions is challenging • Though scores like APACHE III and case-mix indices can provide general comparisons, the nature of the ICU patient population, specialty or focus area of the institution, geographic region, institution size, and other factors can lead to comparisons 'between apples and oranges' when discussing the correct pharmacist-to-patient ratio	• Development of pharmacy specific metric to 'match' ICUs for more direct comparisons • Development of general standards regarding pharmacist-to-patient ratio and staffing models (e.g., evenings, weekends)
5. CCP resource prediction models	• No validated predictive metrics/ or tools for inpatient central pharmacy staffing exist but have significant limitations for application to CCP	• Development of a universally accepted and validated metric for productivity

Table 2. Clinical pharmacy resource prediction tools

Tools	Development	Limitations
Census, patient Acuity, Teaching services, medication Cost, and use of High priority medications (pCATCH): Uses five key components of census, acuity, teaching, cost, and high priority medications to identify areas of highest requirement for pharmacists	• Developed at the University of North Carolina Medical Center to determine the number of clinical pharmacy specialists (CPS) by various medical services • Task force reached a consensus on five key components upon which to base CPS allocation • After applying this methodology to each medical service, the service receives a score from 1 to 5 with five indicating the highest need for CPS, at which time pharmacists were re-allocated	• While a broad staffing model for a large academic medical center with an associated school of pharmacy, it is not specific to a critical care population • Not linked to patient outcomes • Bases patient acuity on diagnosis related group (DRG) • Limited external validity due to its single-center and teaching oriented design. • **Not specific to CCPs**
Pharmacy Intensity Score (PIS): Resource-based relative value intensity grouping system that utilizes pharmaceutical resource consumption data to allocate pharmacy personnel	• Product of number of patients with a specific DRG by specific pharmacy intensity weight (PIW) to calculate pharmacy cost and patient acuity • PIW is calculated by comparing the median pharmacy cost for a given DRG with the median pharmacy cost of all DRGs to determine the 'intensity' of pharmacy resource use in relation to other diagnoses • Gives insight into drug expense at an institution and potentially patient acuity at that site	• Assumes patient acuity is correlated to DRG, which has been shown to not always hold true • Only been used to predict expenditure on resources and not been shown to improved patient outcomes or determine optimal pharmacist-to-patient ratio • Not specific to CCPs
Medication Regimen Complexity Index (MRCI): Provides objective measure of patient-level MRC through dosage form, dosage frequency, and additional medication directions	• Developed from the Medication Complexity Index (MCI) from 134 chronic obstructive pulmonary disorder patient regimens by using an expert panel of 5 researchers scoring six regimens to demonstrate construct/content validity; two researchers scored the same six regimens to determine interrater/test-retest reliability	• Is a patient-oriented, outpatient tool intended to screen for community pharmacist clinical service (vs. those in the ICU) • Not intended to be related to patient acuity or patient outcomes

Table 3. Low, medium, and high quality intervention categories

Low Quality Intervention
• Medication reconciliation with no ADE prevention • Medication route (IV to PO conversion) • Medication route (hypertension management) (medium) • Medication route (hypotension management) (medium) • Discontinuation of clinically unwarranted drugs • Initiation of VTE prophylaxis (medium) • Utilization of most appropriate VTE prophylaxis • Initiation of stress ulcer prophylaxis (medium) • Initiation of VAP prophylaxis (medium) • Antivenom stewardship (medium) • Patient own medication evaluation • Therapeutic interchange • Rejection of a restricted medication
Medium Quality Intervention
• Minor ADE Prevention • Medication reconciliation with minor ADE prevention • Preventing unnecessary labs and/or tests (low) • Prevention of inappropriate screening for heparin-induced thrombocytopenia • Dosage adjusted by pharmacist • Antimicrobial therapy initiation and streamlining • Anticoagulant therapy management • Antimicrobial pharmacokinetic evaluation • TPN management • Emergency Code Blue participation (high) • Rapid Response team participation (high) • Emergency code sepsis participation (high) • Medication teaching or discharge education • Culture follow-up after ED discharge • Prevention of unnecessary high-cost medications
High Quality Intervention
• Major ADE Prevention • Med rec with major ADE prevention • Recommend laboratory monitoring (moderate) • Initiation of or recommendation to initiate a non-antimicrobial therapy (medium) • Bedside monitoring (low) • Emergency code stroke participation • Blood factor stewardship and emergency anticoagulation reversal (medium) • Emergency procedural sedation and RSI participation • Drug information consultation (low) • Drug information consultation – toxicology specific (medium) • Pharmacist-provided drug protocol management pursuant to a collaborative practice agreement

Table 4. Demographic Characteristics

Factor	n = 1,216
Type of Institution	
Academic	991 (88.3)
Community teaching	105 (9.4)
Community non-teaching	26 (2.3)
Region of the United States	
Midwest	389 (34.7)
Northeast	154 (13.7)
South	535 (47.7)
West	44 (3.9)
ICU Type	
Medical	600 (48.8)
Burn	74 (6.0)
Cardiac	12 (0.9)
Cardiovascular Surgery	48 (3.9)
Decentralized/Mixed	132 (10.7)
Neurosciences	228 (18.5)
Surgical	107 (8.7)
Trauma	17 (1.4)
Population Outcomes	
ICU LOS (days), mean (SD)	15.2 (30.6)
Hospital mortality	251 (20.6)
Pharmacist Staffing Information, mean (SD)	
Number of patients provided for on shift	22.8 (18.3)
Number of rounding services covered	1.5 (1.1)
Average interventions per patient	8.4 (4.7)
MRC-ICU	10.4 (6.3)
Practice Area	
Medical	8.4 ± 5.3 (228)
Burn	9.4 ± 4.5 (74)
Cardiac	7.5 ± 5.3 (12)
Cardiovascular surgery	15.4 ± 7.7 (48)
Decentralized/Mixed	9.3 ± 5.0 (132)
Neurosciences	12.4 ± 6.4 (107)
Surgical	9.7 ± 5.7 (17)
Trauma	6.7 ± 4.7 (1.4)
Institution Type	
Academic	10.6 ± 6.6 (991)
Community Teaching	9.7 ± 4.4 (105)
Community Non-Teaching	13.3 ± 4.5 (26)

Table 5. Demographic features and outcomes by MRC-ICU quartile

Factor	MRC 0 – 5 (n = 310)	MRC 6 – 9 (n = 296)	MRC 10 – 14 (n = 289)	MRC ≥ 15 (n = 321)	p-value
Region, n (%)					
Midwest	143 (50.9)	124 (46.1)	63 (24.8)	51 (16.6)	< 0.01
Northeast	48 (17.1)	39 (14.5)	30 (11.8)	35 (11.3)	
South	85 (30.3)	100 (37.2)	136 (53.5)	214 (69.5)	
West	5 (1.8)	6 (2.2)	25 (9.8)	8 (2.6)	
Institution Type, n (%)					
Academic	257 (91.5)	242 (89.9)	207 (81.5)	276 (89.6)	< 0.01
Community teaching	24 (8.5)	22 (8.2)	38 (14.9)	20 (6.5)	
Community non-teaching	0 (0)	5 (1.9)	9 (3.5)	12 (3.9)	
Patient Characteristic, n (%)					
Continuous renal replacement	3 (0.9)	6 (2.0)	35 (12.1)	52 (16.2)	< 0.01
Mechanical ventilation	10 (3.2)	66 (22.3)	157 (54.3)	280 (87.2)	< 0.01
Mechanical circulatory support	0 (0)	2 (0.7)	3 (1.0)	5 (1.6)	0.13
Pharmacist Interventions, mean (SD)					
Interventions per patient	7.6 (4.1)	7.9 (4.3)	8.4 (5.1)	9.8 (5.1)	< 0.01
Intervention quality score	17.2 (16.1)	17.0 (15.9)	18.1 (16.8)	20.2 (16.6)	0.06
Patient Outcomes					
ICU LOS, days, mean (SD)	8.0 (29.9)	10.5 (27.5)	18.2 (36.5)	24.1 (25.6)	< 0.01
Hospital mortality, n (%)	43.0 (14.1)	44.0 (15.0)	66.0 (23.2)	98.0 (30.5)	< 0.01

Table 6. Univariate and multivariate regression of variables related to mortality

	Univariate Analysis			Multivariate Analysis		
Factor	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
MRC-ICU Score	1.08	1.05 – 1.10	< 0.01	1.02	0.98 – 1.06	0.38
Pharmacist-to-Patient Ratio	0.99	0.98 – 1.00	0.03	0.99	0.98 – 1.01	0.24
Acuity						
Continuous renal replacement	5.46	3.54 – 8.45	< 0.01	4.3	2.48 – 7.47	< 0.01
Mechanical ventilation	1.60	1.21– 2.11	< 0.01	0.98	0.63 – 1.52	0.92
Mechanical circulatory support	1.54	0.22 – 7.19	0.61	17.14	1.27 – 231.27	0.03
Institution Type						
Academic	Ref.	---	---	Ref.	---	---
Community teaching	0.27	0.11 – 0.56	< 0.01	0.17	0.04 – 0.71	0.02
Community non-teaching	4.29	1.95 – 9.57	< 0.01	0.21	0.01 – 4.64	0.32
Region						
Midwest	Ref.	---	---	Ref.	---	---
Northeast	0.90	0.50 – 1.57	0.72	0.76	0.35 – 1.63	0.48
South	2.80	1.99 – 4.00	< 0.01	2.73	1.60 – 4.65	< 0.01
West	0.48	0.11 – 1.38	0.23	0.33	0.04 – 2.67	0.30
ICU Type						
Medical	Ref.	---	---	Ref.	---	---
Burn	0.34	0.15 – 0.69	<0.01	0.76	0.32 – 1.82	0.54
Cardiac	0.55	0.08 – 2.13	0.44	1.15	0.13 – 9.97	0.90
Cardiovascular surgery	0.26	0.08 – 0.67	0.01	0.48	0.15 – 1.51	0.21
Mixed	1.23	0.74 – 1.98	0.41	12.59	0.66 – 23.61	0.09
Neurosciences	0.51	0.34 – 0.76	<0.01	0.58	0.33 – 1.02	0.06
Surgery	0.29	0.14 – 0.54	<0.01	0.58	0.33 – 1.02	0.06
Trauma	0	0 – 0	0.97	0.23	0.10 – 0.50	<0.01

Table 7. Univariate and multivariate regression of factors associated with ICU LOS (days)

	Univariate analysis			Multivariate analysis		
Factor	**Δ LOS**	**95% CI**	**p-value**	**Δ LOS**	**95% CI**	**p-value**
MRC-ICU Score	1.10	0.84 – 1.37	< 0.01	0.75	0.32 – 1.19	< 0.01
Pharmacist - Patient Ratio	-0.11	-0.21 – -0.02	< 0.01	-0.03	-0.17 – 0.11	0.71
Acuity						
Continuous renal replacement	6.17	-0.2 – 12.54	0.057	-2.39	-9.21 – 4.42	0.49
Mechanical Ventilation	11.83	8.42 – 15.24	< 0.01	7.44	2.62 – 12.25	< 0.01
Mechanical Circulatory Support	12.52	-7.54 – 32.57	0.22	30.38	1.81 – 58.96	0.04
Institution Type						
Academic	Ref.	---	---	Ref.	---	---
Community teaching	-0.47	-6.79 – 5.86	0.885	1.78	-7.05 – 10.62	0.69
Community non-teaching	32.17	19.91 – 44.43	< 0.01	45.19	21.60 – 68.78	< 0.01
Region						
Midwest	Ref.	---	---	Ref.	---	---
Northeast	5.63	-0.29 – 11.54	0.06	8.35	0.93 – 15.76	0.03
South	6.77	2.61 – 10.91	< 0.01	1.43	-4.33 – 7.20	0.63
West	6.85	-3.30 – 16.73	0.17	6.91	-5.58 – 19.40	0.28
ICU Type						
Medical	Ref.	---	---	Ref.	---	---
Burn	13.70	6.41 – 21.00	< 0.01	15.2	7.06 – 23.35	< 0.01
Cardiac	-8.04	-25.29 – 9.22	0.36	-5.26	-25.53 – 15.02	0.61
Cardiovascular surgery	-5.28	-14.36 – 3.60	0.24	-8.91	-18.27 – 0.45	0.06
Mixed	2.45	-4.27 – 9.18	0.47	-16.17	-36.06 – 3.73	0.11
Neurosciences	-4.80	-9.42 – -0.18	0.04	-5.7	-11.66 – 0.26	0.06
Surgery	4.28	-1.94 – 10.49	0.17	2.68	-4.34 – 9.70	0.45
Trauma	2.40	-12.16 – 16.96	0.74	5.93	-10.01 – 21.86	0.47

Table 8. Univariate and multivariate regression of factors associated with intervention quantity

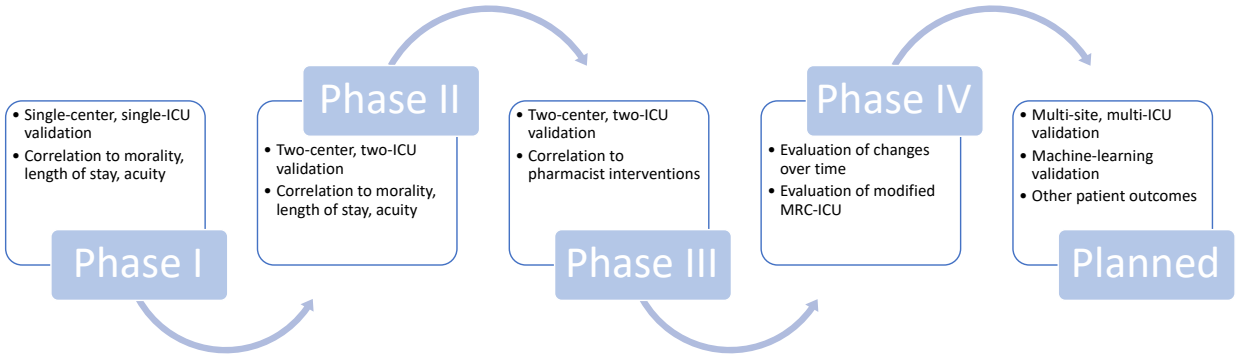
	Univariate Analysis			Multivariate Analysis		
Factor	**β**	**95% CI**	**p-value**	**β**	**95% CI**	**p-value**
MRC-ICU	0.16	0.12 – 0.20	< 0.01	0.11	0.06 – 0.15	< 0.01
Pharmacist-patient ratio	-0.02	-0.04 – -0.01	< 0.01	-0.02	-0.04 – -0.01	0.03
Institution type						
Academic	Ref	---	---	Ref	---	---
Community teaching	0.34	-0.49 – 1.18	0.41	1.42	0.17 – 2.67	0.03
Community non-teaching	1.98	0.37 – 3.60	0.01	-1.81	-5.13 – 1.50	0.28
Region						
Midwest	Ref.	---	---	Ref.	---	---
Northeast	-0.40	-1.16 – 0.36	0.29	-0.57	-1.62 – 0.47	0.28
South	0.89	0.36 – 1.42	< 0.01	0.39	-0.42 –1.20	0.35
West	-2.74	-4.02 – -1.47	< 0.01	-5.04	-6.79 – -3.29	< 0.01
ICU Type						
Medical	Ref.	---	---	Ref.	---	---
Burn	-0.72	-1.83 – 0.39	0.2	0.39	-0.76 – 1.54	0.51
Cardiac	-4.74	-7.36 – -2.12	< 0.01	-0.98	-3.82 – 1.86	0.50
Cardiovascular surgery	2.03	0.68 – 3.38	< 0.01	1.59	0.27 – 2.92	0.02
Mixed	-3.71	-4.73 – -2.69	< 0.01	3.26	0.46 – 6.05	0.02
Neurosciences	-0.26	-0.96 – 0.44	0.47	-0.09	-0.91– 0.73	0.83
Surgery	-0.69	-1.63 – 0.26	0.15	-0.78	-1.76 – 0.21	0.12
Trauma	-0.32	-2.53 – 1.89	0.78	0.95	-1.28 – 3.19	0.40
ICU LOS				-0.01	-0.02 – 0.00	0.05
ICU mortality	-0.85	-1.32 – -0.39	< 0.01	0.82	0.19 – 1.45	0.01

β-coefficients represent change in number of interventions.

Table 9. Univariate and multivariate regression of factors related to intervention quality

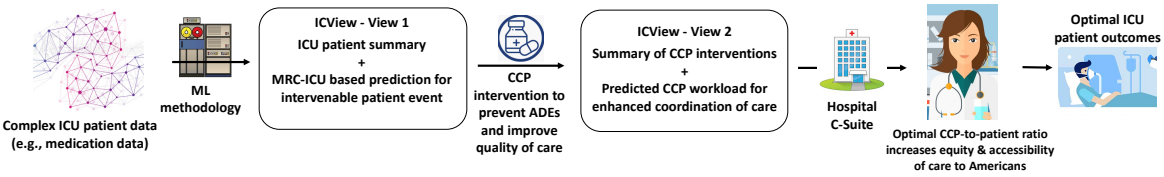
	Univariate Analysis			Multivariate Analysis		
Factor	**β**	**95% CI**	**p-value**	**β**	**95% CI**	**p-value**
MRC-ICU	0.25	0.10 – 0.39	<0.01	0.23	0.05–0.41	0.03
Pharmacist-patient ratio	0.04	-0.02 – 0.09	0.18	0.07	-0.01–0.16	0.11
Institution type						
Academic	Ref.	---		Ref.	---	0.79
Community teaching	2.29	-0.97 – 5.54	0.17	4.93	-6.67 – 16.52	
Community non-teaching	1.1	-5.21 – 7.41	0.73	-8.39	-27.54 – 10.77	
Region						<0.01
Midwest	Ref.	---		Ref.	---	
Northeast	2.01	-1.00 – 5.02	0.19	-0.24	-4.56 – 4.08	
Southeast	1.8	-0.30 – 3.91	0.09	1.62	-2.43 – 5.68	
West	-7.2	-12.22 – -2.17	0.01	-13.94	-21.23 – -6.64	
Closed	4.02	-0.77 – 8.81		5.2	-1.05 – 11.44	
ICU Type						0.06
Medical	Ref.	---		Ref.	---	
Burn	0.75	-3.15 – 4.66	0.71	6.63	0.96 – 12.31	
Cardiac	-10.12	-19.36 – -0.88	0.03	-2.87	-14.12 – 8.37	
Cardiovascular surgery	2.99	-1.77 – 7.74	0.22	1.01	-4.24 – 6.26	
Mixed	-8.48	-12.08 – -4.88	<0.01	7.06	-9.26 – 23.38	
Neurosciences	3.26	0.79 – 5.73	0.01	3.51	0.15 – 6.87	
Surgery	1.17	-2.16 – 4.50	0.49	4.37	-0.61 – 9.35	
Trauma	-0.1	-7.90 – 7.69	0.98	5.55	-3.90 –15.00	
ICU LOS	0.01	-0.02 – 0.04	0.63	-0.01	-0.05 – 0.02	0.39
ICU mortality	0.53	-1.75 – 2.82	0.65	0.67	-1.85 – 3.19	0.60

Figure 1. MRC-ICU Research Pathway



A strength to the use of a more universal predictor of patient outcomes and pharmacist resources, such as medication regimen complexity, is the ability to compare models among institutions.

Figure 2. Construct for machine learning methodology applied to the MRC-ICU Scoring Tool

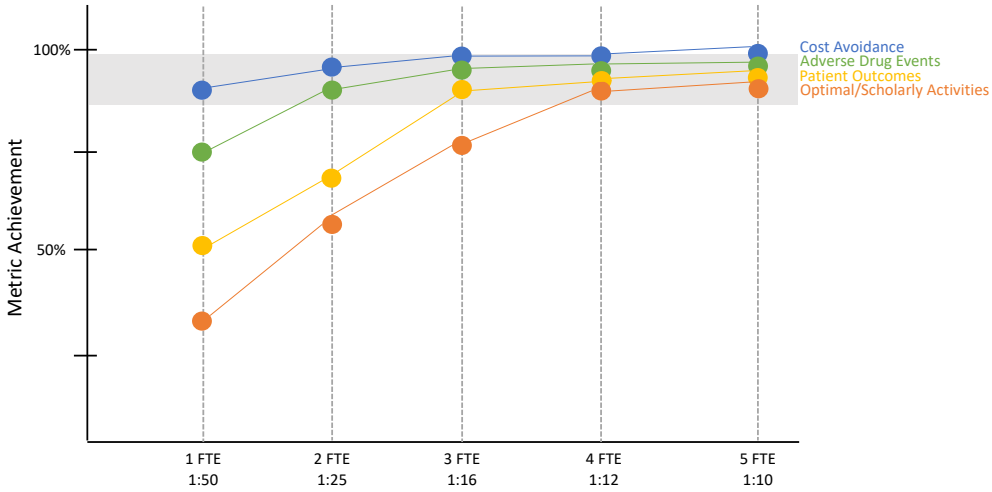


Here, machine learning methodology creates multiple 'views' within a health information technology tool available to clinicians. This machine learning based analysis of medication regimen complexity, in addition to other pertinent patient characteristics, could predict pharmacist activity and avoid adverse outcomes. Further, by summarizing these data, administrators have the power to optimize their workforces.

Appendix 1. MRC-ICU Scoring Tool

Parameter	Value	Points
High Priority Medications		
Aminoglycosides (amikacin, gentamicin, tobramycin)	3x	
Amphotericin B and Liposomal Amphotericin B	1	
Antiarrhythmics (amiodarone, dofetilide, sotalol)	1x	
Anticoagulants (NOAC's/DOAC's, fondaparinux)	1x	
Anticonvulsants (carbamazepine, phenobarbital, phenytoin, valproic acid)	3x	
Argatroban	2	
Azole antifungals (posaconazole, voriconazole)	2x	
Blood Products (Factor products, Antithrombin III)	2x	
Chemotherapy (active inpatient)	3x	
Clozapine	3	
Digoxin	3	
Ganciclovir/valganciclovir	1x	
Hyperosmolar fluids (hypertonic saline (1.5%, 3%, 23.4%), mannitol)	1x	
Immunosuppressants (cyclosporine, sirolimus, tacrolimus)	3x	
Lidocaine (continuous infusion)	2	
Lithium	3	
Prostacyclins (epoprostenol, iloprost, treprostinil)	2x	
Theophylline	3	
Therapeutic heparins (enoxaparin, heparin infusion)	2x	
Vancomycin (IV)	3	
Warfarin	3	
Neuromuscular Blockade	2	
Continuous infusions (exclude those listed elsewhere)	1x	
Total Parenteral Nutrition		
Managed by non-pharmacist service	1	
Managed by clinical specialist pharmacist	3	
ICU Prophylaxis and FAST HUGS BID		
Thromboembolic prophylaxis	1	
Stress ulcer prophylaxis (exclude pantoprazole infusion)	1	
Glycemic control (subcutaneous insulin; exclude IV insulin)	1	
Bowel regimen	1	
Chlorhexidine	1	
Analgesia and Sedation		
Opioids and sedatives (scheduled and PRN)	1x	
Continuous infusion opioids and sedatives	2x	
Antimicrobial Agents		
Antimicrobials (include HIV medications, exclude those listed elsewhere)	1x	
Restricted antimicrobials	2x	
Devices		
Dialysis	2	
Extracorporeal membrane oxygenation (ECMO)	2	
Intra-aortic balloon pump (IABP) / Left ventricular assist device (LVAD)	1	
Mechanical ventilation	2	
Total Score		
X indicates a multiplier for points per medication.		

Appendix 2. Pharmacist to patient ratio vs. outcomes of interest



Ultimately, evaluation of pharmacist productivity (and associated return on investment) is based on the specific metric of interest. For example, with cost avoidance, this goal may be achieved with the addition of a single pharmacist, meaning that any further resources will actually reduce ROI. However, if metrics like scholarly activities as outlined in the position statement are used, this ROI may increase for each additional employee.

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