Published in final edited form as:

Leuk Lymphoma. 2018 June ; 59(6): 1498–1500. doi:10.1080/10428194.2017.1376744.

Predictive performance of early warning scores in acute leukemia patients receiving induction chemotherapy

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Keywords

Leukemia; Induction Chemotherapy; Infection; Critical Care

Acute leukemia is a family of clonal hematopoietic disorders characterized by genetic and epigenetic alterations leading to a block in differentiation and accumulation of leukemic blasts in blood and bone marrow [1]. The long-term overall survival rates vary according to age as well as molecular and cytogenetic prognostic factors, but remain poor for some patients despite intensive treatment [2]. The clinical course of remission induction is complex, and patients are at risk for numerous complications including infection, bleeding, and metabolic abnormalities. During induction chemotherapy, patients with acute leukemia are at particularly high risk for infection due to underlying immune defects as well as myelosuppression from chemotherapy. More than 80% of patients will develop fever, and an infectious cause is identified in 20–30% of cases [3]. The widespread use of prophylactic antimicrobials has improved infection-related and all-cause mortality [4]. However, many patients continue to suffer adverse outcomes from infection, and early institution of antibiotic therapy leads to improved outcomes [5].

Early warning scores have been developed to improve the outcomes of hospitalized patients by facilitating early recognition of critical illness [6]. In 2007, the National Institute for Health and Clinical Excellence of the United Kingdom recommended that early warning scores be used to monitor all adult hospitalized patients [7]. In 2012, the Royal Colleges of Physicians recommended that a new National Early Warning Score be used to monitor all adult patients in both prehospital and hospital settings [8]. Most recently, The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) introduced a new tool called the quick Sepsis-related Organic Failure Assessment (qSOFA) score [9]. However, the performance of early warning scores in many specialized populations remains

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unclear. The purpose of this study was to evaluate the predictive performance of the Modified Early Warning Score (MEWS) [10] and qSOFA in acute leukemia patients receiving induction chemotherapy.

We performed a retrospective cohort study of patients with acute leukemia who were admitted for induction chemotherapy between October, 1 2011 and December 31, 2015 at The Ohio State University Wexner Medical Center. This study was approved by The Ohio State University Institutional Review Board with a waiver of informed consent. We included those patients with probable infection outside the ICU. Probable infection was defined as a positive result on any test designed to detect pathogens including body fluid culture and polymerase chain reaction (PCR). The PCR tests included tests for respiratory viral pathogens and toxigenic *Clostridium difficile*. We excluded patients with missing data. We manually reviewed the electronic health records of all included patients. Vital signs and nursing assessment of mental status by the Richmond Agitation-Sedation Scale (RASS) [11] were obtained automatically through The Ohio State University Information Warehouse. The primary outcomes of the study were ICU admission and in-hospital mortality.

MEWS was calculated as shown in Table 1 [10]. qSOFA was calculated by assigning one point each for each for altered mentation, respiratory rate $\geq 22/\text{min}$, and systolic blood pressure $\leq 100 \text{ mmHg}$ [9]. The MEWS and qSOFA scores were calculated for each patient for each day of their hospitalization using the most abnormal physiologic parameters for each day. The maximum score for each patient from 48 hours prior to the development of probable infection to 24 hours following was then included in subsequent analysis. This time window was used since clinical deterioration may begin before, during, or after the moment when infection occurs [9]. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using multiple thresholds for the assessment of ICU admission and in-hospital mortality. We assessed the discrimination of both scores for each outcome by calculating the area under the receiver operating characteristic curve (AUROC). We considered AUROCs to be poor between 0.60 and 0.70, fair between 0.70 to 0.80, good between 0.80 and 0.90, and excellent between 0.90 and 1.00 [12]

Five hundred and sixty-eight patients with acute leukemia were admitted for induction chemotherapy between October of 2011 and December of 2015 at our institution. The mean (standard deviation) age of the patients was 53.8 (15.1) years. The most common type of leukemia was acute myeloid leukemia (AML) (n=366 [64%]) followed by acute lymphoblastic leukemia (ALL) (n=107 [19%]), acute promyelocytic leukemia (APL) (n=52 [9%]), and mixed phenotypes (n=11 [2%]). Among the 568 patients admitted for induction chemotherapy, 64 patients were excluded for missing data. Thus, we had 504 patients available for analysis. Among those 504 patients, 211 (42%) developed probable infection during their hospitalization. Further investigation revealed that 49 (23%) patients with probable infection were admitted to the ICU and 14 (7%) died in the hospital.

The predictive performance of MEWS and qSOFA for both outcomes was determined as shown in Table 2. We used thresholds of ≥ 5 for MEWS and ≥ 2 for qSOFA since those are the most commonly used thresholds in clinical practice [13]. We found that there was no

statistically significant difference between the AUROCs of MEWS and qSOFA ($p=0.93$ for ICU admission and $p=0.20$ for in-hospital mortality). Both MEWS and qSOFA demonstrated good discrimination for ICU admission with AUROCs of 0.82 (95% CI 0.75–0.90) and 0.83 (95% CI 0.76–0.89), respectively. MEWS had good discrimination for in-hospital mortality (AUROC 0.82, 95% CI 0.71–0.92), whereas qSOFA had fair discrimination for in-hospital mortality (AUROC 0.76, 95% CI 0.63–0.88). Both scores had relatively high sensitivity and negative predictive value, but they were limited by low specificity and positive predictive value. The performance of both scores varied according to the subtype of acute leukemia.

We used RASS to assess mental status because it is routinely calculated on all patients at our medical center. However, Subbe et al. [10] used the Alert Voice Pain Unresponsive scale, and Seymour et al. [9] used the Glasgow Coma Scale. It is possible that our use of RASS affected the predictive performance of the early warning scores in our study. However, Seymour et al. [9] tested qSOFA with different assessments of mental status and obtained similar results each time. Other studies have used different assessments of mental status with similar results as well [13]. It may be the case that changes in mental status from baseline are more important than absolute changes in mental status [9], but MEWS and qSOFA do not differentiate between those concepts.

Another limitation of our study is how we identified patients who were likely to be infected. qSOFA was originally studied in a cohort of patients who met a specific definition of suspected infection [9]. We studied qSOFA in a different cohort of patients who had positive cultures and PCR tests. Since positive results may reflect colonization or contamination of samples rather than infection, it may not be accurate to label all patients with positive results as definitely infected. For example, our definition of probable infection included patients with positive blood cultures growing coagulase-negative staphylococci. Additionally, some patients without positive cultures and PCR tests may actually be infected. Other studies have used different definitions of suspected infection with similar findings [14,15].

In conclusion, this is the first study to investigate the performance of early warning scores in acute leukemia patients. We found that MEWS and qSOFA predicted adverse outcomes with good discrimination in acute leukemia patients with probable infection. Since there was no statistically significant difference between the AUROCs of both scores, our results suggest that either score may be used in clinical practice. This finding is important because MEWS and its derivatives are commonly used throughout the world including at our institution where MEWS is fully integrated into the electronic medical record. qSOFA continues to receive attention as a possible alternative to the Systemic Inflammatory Response Syndrome for early identification of patients with sepsis [15]. Although it remains unknown whether the implementation of early warning scores improves outcomes, such implementation may help facilitate early recognition of critical illness. Connecting early warning scores to specific interventions such as rapid response teams may allow for the highest potential to improve patient care [6].

Acknowledgments

Disclosures

This study was supported by The Ohio State University Comprehensive Cancer Center, which is funded by the National Cancer Institute of the National Institutes of Health under award number P30CA016058.

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Table 1.

MEWS [10]

Observation	3	2	1	0	1	2	3
Respiratory rate (breaths/min)		< 9		9–14	15–20	21–29	>29
Heart rate (beats/min)		<40	41–50	51–100	101–110	111–129	> 129
Systolic BP (mm Hg)	<70	71–80	81–100	101–199		>199	
Temperature (°C)		<35		35–38.4		>38.4	
Neurologic				Alert	Voice	Pain	Unresponsive

The points for each observation are added to obtain the total score.

Table 2.

Predictive performance of MEWS and qSOFA for ICU admission and in-hospital mortality

Score	Outcome	Sensitivity	Specificity	PPV	NPV	AUROC
MEWS	ICU Admission	0.88 (0.75–0.95)	0.56 (0.48–0.64)	0.38 (0.29–0.47)	0.94 (0.87–0.98)	0.82 (0.75–0.90)
	In-Hospital Mortality	0.93 (0.66–1.00)	0.49 (0.42–0.56)	0.11 (0.06–0.19)	0.99 (0.94–1.00)	0.82 (0.71–0.92)
qSOFA	ICU Admission	0.82 (0.68–0.91)	0.69 (0.61–0.76)	0.44 (0.34–0.55)	0.93 (0.86–0.97)	0.83 (0.76–0.89)
	In-Hospital Mortality	0.79 (0.49–0.95)	0.59 (0.52–0.66)	0.12 (0.06–0.21)	0.98 (0.93–0.99)	0.76 (0.63–0.88)

Each estimate is presented with its associated 95% confidence interval.