INVESTIGATING THE PROGNOSTIC IMPORTANCE OF BIOELECTRICAL IMPEDANCE STANDARDIZED PHASE ANGLE IN ADULTS TREATED FOR NEWLY DIAGNOSED ACUTE LEUKEMIA

BY

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LIST OF ABBREVIATIONS

ADL Activity of daily living

ALL Acute lymphoblastic leukemia

AML Acute myeloid leukemia

BCM Body cell mass

BIA Bioelectrical impedance analysis

BMI Body cell mass

BUN Blood urea nitrogen

CCI Charlson comorbidity index

CGA Complete geriatric assessment

CN-AML Cytogenetically normal acute myeloid leukemia

CR Complete remission

CRi Complete remission with incomplete count recovery

CRP C-reactive protein

DNF Duration of neutropenic fever

ECF Extracellular fluid

ECOG PS Eastern cooperative oncology group performance status

ELN European leukemia network

ETP ALL Early T-cell precursor acute lymphoblastic leukemia

FLT3-ITD FLT3 internal tandem duplication

HCT-CI Hematopoietic cell transplantation comorbidity index

HR Hazard ratio

HSCT Hematopoietic stem cell transplant

IADL Independent activities of daily living

ICF Intracellular fluid

KPS Karnofsky performance status

LHS Length of hospital stay

MDS Myelodysplastic syndrome

NSCLC Non-small cell lung cancer

OR Odds ratio

OS Overall survival

PG-SGA Patient-generated subjective global assessment

PH+ Philadelphia positive

PhA Phase angle

PS Performance status

SGA Subjective global assessment

SPhA Standardized phase angle

SPPB Short physical performance battery

TBW Total body water

TRM Treatment related mortality

WBC White blood cell count

ABSTRACT

We investigated the predictive value of standardized phase angle (SPhA) on 60-day mortality, overall survival (OS), and length of hospital stay (LHS) for adults with acute myelogenous and lymphoblastic leukemia (AML and ALL). Phase angle measurements were taken on day 1 of induction therapy for all patients and again on the day of nadir bone marrow for AML patients only. Measurements were standardized by BMI, gender, and age to calculate the SPhA. The difference between SPhA at nadir bone marrow and day 1 of induction was used to calculate change in SPhA. A cut off of 25th percentile was used to dichotomize SPhA. Cox proportional hazards models were fit for SPhA and change in SPhA as predictors of OS and LHS while logistic regression models were used to assess 60-day mortality. Among 100 patients 88% were AML, 56% were female, and mean age was 59 years. SPhA was associated with 60-day mortality in univariable (OR=5.25; 1.35, 20.40; P=0.02) but not multivariable analysis (OR=3.12; 0.67, 14.48; P=0.15) adjusted for age, creatinine, and cytogenetics. Change in SPhA was associated with OS (HR=1.16; 1.01-1.34; P=0.04) in multivariable analysis. Standardized phase angle is an objective measure that may be used to inform risk stratification.

Chapter 1

Background and Epidemiology:

The acute leukemias in adulthood are comprised of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), a group of aggressive, molecularly heterogeneous malignancies characterized by malignant, clonal proliferation of myeloid and lymphoid precursor cells, respectively. The resultant proliferation of these abnormal cells leads to bone marrow failure and eventually death due to the associated sequelae of the loss of all cell lines of the hematopoietic-tree. The most recent NIH SEER Cancer Statistics data showed, in the age group of 55-85+ years old, approximately 19,000 new cases of acute leukemia between 2011-2015 with AML making up 79% of those cases [(1)]. AML primarily affects older adults (≥60 years) with a median age at diagnosis of 67 years [(1)]. Due to its peak incidence at 1-4 years old, ALL is often perceived as a malignancy of children. However, there is another gradual increase in incidence in adults starting at 45 years of age and continuing into the older adult population [(1)]. Unlike in the pediatric population where intensive chemotherapy has produced cure rates approaching 90%, ALL in adults remains a tremendous challenge with 5-year survival rates for those 40-75+ years old between 9.1-38.9% [(2) (1, 3)]. The same can be said for AML in both the adult and older adult population where the 5-year survival rates for AML patients 40-64 years and ≥65 years are 37.9% and 7.1%, respectively [(1)].

Prognostic Factors in the Acute Leukemias: Tumor and Patient-Specific Factors

Therapy decisions for patients with acute leukemia are of the utmost importance and must balance the individual patient's chance of success with their likelihood of treatment

related morbidity and mortality (TRM). Much work has been done in the last few decades regarding factors that allow the clinician to predict outcomes for patients presenting with acute leukemia. Key outcomes commonly studied are overall survival (OS), complete remission (CR), and TRM. Prognostic factors in the acute leukemias can be separated into patient-related factors and tumor-specific factors. The combination of these prognostic factors has led to multiple scoring systems that assist the clinician in predicting a patient's prognosis for a given treatment.

Prognostic Factors in the Acute Leukemias: Tumor Specific Factors

Tumor-specific prognostic factors for acute leukemia include cytogenetics and gene mutations. Cytogenetics is accepted as the single most important prognostic factor for AML and a crucial prognostic factor for ALL [(3) (4)]. In AML, numerous cytogenetic abnormalities have been described leading to various cytogenetic risk classifications systems to predict OS. In 1998, Grimwade et al conducted one of the largest studies regarding cytogenetics and prognosis where they were able to categorize 3 cytogenetics risk groups favorable: t(8;21), t(15;17) or inv(16), intermediate: 11q23 abnormalities, +8, +21, +22, del(9q), del(7q), and all other structural or numerical defects not encompassed by the favorable or adverse risk groups, adverse: presence of a complex karyotype, -5, del(5q), -7, or abnormalities of 3q) with associated 5-year survivals of 65%, 41%, and 14% (P<.001) [(5)]. Since this time many studies have been conducted resulting in revision of classification of specific cytogenetic patterns (e.g 11q23 and del(7q) are now known to be adverse), discovery of new cytogenetic abnormalities, and incorporation of information on the prognostic significance of specific gene mutations. Gene mutations allow for understanding of the genetic diversity within the cytogenetic groups, especially the large and heterogeneous group of patients with cytogenetically normal AML (CN-

AML) [6]. Within CN-AML, the three mutations that have most consistently and significantly proven to be prognostic for various response and survival outcomes are NPM1, CEBPA, and FLT3 [6]. Patients with CN-AML with internal tandem duplication of the FLT3 gene (FLT3-ITD) have worse outcomes compared with those without FLT3-ITD. NPM1 mutation in CN-AML is associated with higher CR rates as well as better event free survival and relapse-free survival [6, 7]. 40% of patients with NPM1 also have FLT3-ITD which, when taken together, confers a negative prognosis. The gene-gene interaction of NPM1 with FLT3-ITD illustrates the context dependent nature of genetic mutations in AML: the prognostic impact of many markers is dependent on the presence or absence of another mutation. Biallelic CEBPA mutations also confer a favorable prognosis with survival data similar to patients with NPM1 without FLT3-ITD. In 2010, an expert panel with the European Leukemic Network (ELN) incorporated the cytogenetic and gene mutation research into a 4 group (Favorable, Intermediate-I, Intermediate-II, and Adverse) risk classification [6]. The validation of the prognostic significance of this system was subsequently studied in three follow up studies and the results of these studies have led to the modification of the 2010 ELN scoring system to the most recent 2017 version [8] [9, 10].

Cytogenetics and genetic mutations are similarly prognostic in ALL. Within B-Cell ALL, making up 75% of ALL in adults, two important subgroups are BCR/ABL+ (Ph+) and BCR/ABL-like ALL. Ph+ ALL is characterized by leukemia cells harboring the Philadelphia Chromosome t(9;22) which leads to a constitutively active BCR-ABL tyrosine kinase and resultant extreme cell proliferation. With the advent of Tyrosine Kinase Inhibitor therapy, prognosis in Ph+ ALL has improved significantly [2]. Ph-like ALL is a unique entity characterized by gene expression similar to Ph+ ALL, a multitude of genetic alterations causing activation of tyrosine kinases, mutation of lymphoid transcription factor genes, and poor outcomes compared to Ph+ ALL. T-cell ALL,

accounting for 25% of ALL in the adult population, has similar outcomes to B-cell ALL in adults. It is a genetically heterogeneous disease requiring information on chromosomal translocations, DNA duplications and deletions, mutations, and reregulated gene expression to categorize the most frequent lesions. A unique entity within T-Cell ALL is early T-Cell precursor ALL (ETP ALL), which is easily recognized by flow cytometry due to its distinct immunophenotype. Many mutations have been identified within early T-cell precursor ALL with early evidence suggesting similar genomic background to AML. Similar to AML, the prognosis for ETP ALL is quite poor [(2) (11) (12)].

Despite their significant prognostic influence, there are limitations to cytogenetics and genetic mutations. Regarding cytogenetics, Grossman et al noted that 20-30% of AML cytogenetics are rare and thus their prognostic significance can only be examined in very large data sets. Furthermore, 45% of AML are CN-AML and thus cannot be further subdivided by their cytogenetics even though they are clinically a highly heterogeneous group [(13)]. Cytogenetic and mutation data also may take >1 week to become available, leading to dilemmas for the clinicians who may need to start treatment immediately. Several studies have looked at whether there are worse outcomes for AML patients with longer time from diagnosis to treatment and have shown no effect for older adults but are inconclusive in younger (<60) patients [(14) (6) (15)].

Prognostic Factors in the Acute Leukemias: Patient-Specific Factors

Patient-specific prognostic criteria in acute leukemia include age, performance status, comorbidities, and geriatric assessment. While it has come into question whether age is the most powerful patient-related prognostic factor in the leukemias, its significance is noteworthy [(4)]. The mechanisms by which advanced age contributes to a patient's prognosis are many. Older acute leukemia patients have higher frequencies of adverse cytogenetics with lower frequencies

of favorable ones, increased expression of multi-drug resistance efflux pumps, and increased secondary AML following Myelodysplastic Syndrome (MDS) or cytotoxic treatment [11, 16] [17]. Advanced age is associated with a higher frequency of comorbidities [16], leading to contraindications against intensive chemotherapy. Additionally, interactions of patient's medications for their comorbidities with their chemotherapy is possible. Finally, there is a higher frequency of worse performance status (PS) [16] [11]. After controlling for all these variables age is still independently prognostic [18]. Similarly, Applebaum et al found, in adults>65 years of age treated with intensive chemotherapy, outcomes continued to worsen with increasing age even when controlling for cytogenetics [17]. These findings make the argument that the leukemias in older adults are a unique biological entity when compared to those of younger patients [17] [19].

Patient-Specific Factors: Performance Status

PS is a measure of a patient's physical function. In oncology, one of two PS scales, the Eastern Cooperative Oncology Group (ECOG PS) or Karnofsky Performance Status (KPS), is commonly used. PS is a particularly useful measure in distinguishing those who will not tolerate induction with intensive chemotherapy, as high ECOG PS scores (3-4) predict a decreased chance of deriving benefit from the therapy and a higher likelihood of toxicities [20] [17, 21]. PS remains independently prognostic when controlling for common covariates, including age [22] [23]. Importantly, the prognostic importance of PS increases with increasing age. This was demonstrated in a 2006 study by the Southwest Oncology Group showing 30-day mortality rates for patients with an ECOG PS score of 0 were only modestly different (11-15%) for differing ages (55-65,66-75, and >75). In these same age groups with an ECOG=3, the 30-day mortality rates ranged from 29%, 47%, and 82% [17]. A study of 998 patients >65 years treated with intensive

induction regimens found a similar result for OS, where OS at one year was 35%, 25%, and 7% for ECOG PS 1,2, and 3, respectively [24].

The main limitations to PS scales are that they lack sensitivity and are highly subjective. Practically speaking, PS scales lack the ability to distinguish those who are fit (similar treatment tolerance to middle-aged patients) from vulnerable (those at higher risk of toxicity), but do have the ability to distinguish those two categories from frail patients (those likely to experience significant toxicity) [25]. For example, a study of older adults treated with intensive chemotherapy by Klepin et al showed, among patients with ECOG 0 or 1, the identification of significant physical impairments, with 48% impaired in activities of daily living (ADLs) and 54% impaired in objectively tested physical performance [26]. Similarly, a prospective study of newly diagnosed AML patients by Wedding et al found that those with reported impairments in independent activities of daily living (IADLs) had worse OS independent of PS score and age [27]. Another study of newly diagnosed MDS and AML patients found that those requiring assistance with ADLs had shorter OS independent of age, cytogenetics, and KPS [28]. A final limitation mentioned by Ostgard et al is that patients with acute leukemia often present with severe, acute symptoms which rapidly lowers their functional status. In this setting, the functional PS score given at time of diagnosis is more a reflection of their leukemia severity than normal functional [29].

Patient-Specific Factors: Comorbidities

Older acute leukemia patients commonly have comorbidities [11] [30] [31]. Comorbidity score is currently measured using either the Charlson Comorbidity Index (CCI) or the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI). Although both appear to be an appropriate tool for comorbidity assessment, the HCT-CI includes additional conditions

compared to the CCI. To illustrate the prevalence of comorbidities in this population, in a study using SEER Cancer statistics containing over 5,000 individuals with AML (median age=78 years) half of them had at least one comorbidity based on claims data [30]. Even higher numbers (70-80%) have been found in the older adult ALL population [3]. Although the prevalence of comorbidities in this population is not disputed, the prognostic significance of comorbidities is still debated. Ostgard et al found after adjusting for other known covariates (age, cytogenetics, PS, etc…), intensively treated AML patients with CCI score 1 and ≥2, had no difference in short term (90 day) mortality compared to patients with CCI=0, with mortality rate estimates and 95% CIs of 1.09 (0.76;1.56) and 0.96 (0.55;1.96), respectively [29]. In comparison, Etienne et al, in a retrospective study of 133 older adult patients receiving intensive induction chemotherapy, found CCI (compared to a value ≤1) was independently prognostic for CR (CCI>1 OR=0.29, p=0.05) [32]. The previously mentioned population study utilizing SEER data found similar findings for the outcomes of OS and 8-week mortality [30]. As pointed out by multiple authors, despite some disagreement between studies, the available evidence as well as clinical expertise supports comorbidity as a negative prognostic factor and thus the importance of collecting such data [25] [3].

One key limitation of comorbidities is that many clinical trials for AML do not capture comorbidity data and, despite the scoring tools mentioned above, some do not utilize standardized indices to capture data [3] [25]. Furthermore, questions remain regarding how to adjust treatment plans based on comorbidity burden as well as the prognostic significance of individual conditions [20].

Patient-Specific Factors: Complete Geriatric Assessment

Due to a recognition of the shortcomings of PS, comorbidity scores, and age as individual prognostic factors, Complete Geriatric Assessment (CGA) has been developed to be a more thorough tool to account for the complexities of prognostication in the older acute leukemia patient. CGA attempts to adequately assess a patient's fitness by evaluating multiple patient characteristics (physical function, comorbidities, cognitive function, psychological state, social support, polypharmacy, and nutritional status) to allow for the differentiation of fit, vulnerable, and frail patients [20]. In a prospective, single institution study involving adults ≥ 60 years with newly diagnosed AML and treated intensively, CGA was found to both be feasible and to detect significant variability in valuable patient characteristics that are not routinely captured [26]. Specifically, even among those with ECOG PS 0-1, impairments in cognition (24%), physical performance (31%), and ADLs (34%) were found, along with distress (50%), depression (26%), and comorbidities (using the HCT-CI) (40%). Most patients had 1 (92.6%) or more (63%) impairments. CGA has also been found to be prognostic in intensively and non-intensively treated AML patients and is suspected to be prognostic in older adult ALL patients as well [3, 28, 31, 33]. Sherman et al, utilizing registry data to collect CGA parameters, retrospectively studied 101 older adult, newly diagnosed AML patients who were either intensively or non-intensively treated. They found, when controlling for other covariates including cytogenetics and secondary AML, difficulty with strenuous activity (HR=2.18; 95% CI 1.19-4.00), pain (HR=2.17; 95% CI 1.19-3.97), and comorbidity score (HR=1.92; 95% CI 1.18-3.11) were independently prognostic for OS even when patients were ECOG PS 0-1 [33]. Similarly, a study of 107 non-intensively treated newly diagnosed AML and MDS patients found ADLs<100 (HR=2.94), KPS<80 (HR=2.34), and quality of life or 'fatigue' (HR=1.77) all to be independently prognostic for OS. Utilizing these three variables the authors created a fitness scoring system with low (0), intermediate (1-2), and high (3) risk categories which predicted variable OS for each group (774, 231, and 51 days,

respectively, p<0.01) [28]. Finally, in 74 intensively treated, newly diagnosed AML patients, Klepin et al, using standardized indices for physical (assessed via self-reporting and Short Physical Performance Battery, SPPB) and cognitive function (MMSE and 3MS), among other measures, found cognitive (3MS score<77, HR=2.5; 95% 1.2-5.5) and physical (SPPB score<9, HR=2.2; 95% CI 1.1-4.6)) function to be independently prognostic for OS after adjusting for common covariates (age, gender, ECOG PS, cytogenetics, prior MDS, and hemoglobin) [31].

The fact that many of the measures collected in CGA are highly modifiable make it not only a predictive tool but one that may direct interventions to better a patient's chances of tolerating chemotherapy. For example, if a patient were to score low in physical performance, would an intervention improving one's physical performance lower their risk of early mortality? This question is currently being examined [20]. Other theoretically intervenable measures are nutrition status, management of comorbid disease, polypharmacy, symptom burden, and fatigue. Continued work needs to be done in CGA regarding validation in large, multisite trials with uniform treatment approaches, specifically focusing on the most predictive and efficient CGA measure to be used in clinical practice [25].

Prognostic Scoring Systems in adult ALL and AML

The standard of care for treatment of both AML and ALL has remained, for many years, intensive chemotherapy and stem cell transplant. However, particularly in the older adult population, there remains considerable disagreement on whether patients should receive intensive chemotherapy, or instead receive low intensity chemotherapy or best supportive care, due to fear of TRM from treatment [3, 21, 22].In a retrospective study conducted in 2016 by Ma et al evaluating the treatment patterns of US community oncology practices in newly diagnosed, older adult AML patients, only 5 patients (0.5% of cohort) were given standard induction

chemotherapy, and 43% of patients did not receive any definitive leukemic therapy at all [34]. In a study by Juliusson et al using population data from the Swedish Acute Leukemia Registry, 30-day mortality rates were improved in those treated with intensive chemotherapy versus palliation alone in all age groups and PS levels [22]. Furthermore, improvements in supportive care and better health statuses of patients have led to decreases in TRM [35]. However, Kantarjian et al argued that all newly diagnosed AML patients ≥ 70 years, except a small (28%) subset of patients with favorable karyotype and 0/4 adverse risk factors (i.e. patients with Age<80, PS 0-1, non-complex karyotype, and creatinine level ≤ 1.3), should not receive intensive chemotherapy due to the unacceptably high 8-week mortality rate (36%). In these patients they suggest low intensity therapy or clinical trials comparing low intensity to high intensity chemotherapy [21]. Few randomized trials have been done to analyze this question, but findings suggest that older patients, if medically fit, may benefit from intensive therapy [4].

There is widespread agreement that there is a subset of AML patients who should receive low-intensity therapy. There is also agreement that a baseline assessment of risk of TRM is necessary before treatment decisions are made. This assessment ought to occur in all AML patients, as older age should not be used as the only factor as it has been shown not to be the most important predictor of TRM [7, 21, 31]. A number of assessments, in the form of prognostic scoring systems, have been proposed using a combination of data regarding 1) characteristics of the malignancy, 2) laboratory and clinical variables, and 3) patient characteristics, with the exception of CGA. In the Kantarjian study, karyotype, creatinine, age, and ECOG PS were predictive of 8-week mortality ranging from 16%, 31%, 55%, and 71% in those with 0,1,2, and ≥3 risk factors, respectively [21]. Krug et al created a model for 60-day mortality incorporating presence of secondary AML or prior hematologic disease, molecular/cytogenetic risk, body temperature, hemoglobin platelets, LDH, fibrinogen, white blood cell count (WBC), presence of

infection, and age. They found when cytogenetic and molecular risk data was present predictions of TRM ranged from 6-69% [18]. Finally, Wheatley et al utilized cytogenetic risk group, presence of secondary AML, WBC, age, and ECOG PS to define good, standard and poor risk groups, with 1-year survival of 53%, 43% and 16% respectively [36]. While promising, these scoring systems rely primarily on patient age as a surrogate measure for key patient specific factors, such as comorbidity, physical function, cognition, and nutritional status, that are known to vary among individuals of the same age [25]. Furthermore, none of these systems utilize CGA. These limitations are brought up by authors of these studies [18], the most recent ELN 2017 guidelines, and multiple other reviews [4] [7, 37]. Finally, Ossenkoppele et al point out an inherent limitation of all these scoring systems in that they are all created from data collected from all intensively treated patients which is not reflective of the real world older AML population [7].

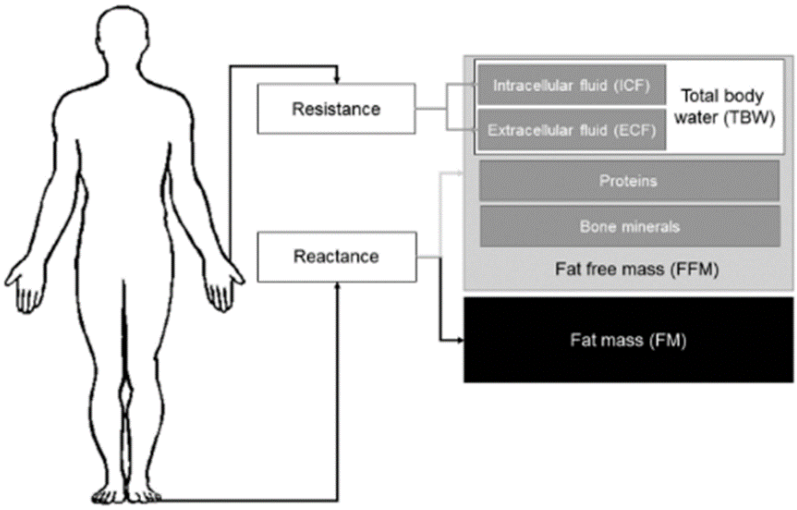
The combination of these limitations account, in part, for the incomplete acceptance of these risk scoring systems leading, in the end, to a lack of consistent treatment practices for older adults with acute leukemia. The previous discussion can similarly be applied to the older ALL population where, despite our understanding of many prognostic factors, no consensus exists on the specific risk criteria and terminology for defining prognostic subgroups. Several factors have led to this problem. For one, ALL is a heterogeneous disease with many distinct subtypes making it difficult to develop a uniform approach. Furthermore, Gokbuget notes the vicious cycle in adult ALL where poor results in treatment have led to a lack of large randomized prospective trials from which outcomes can be reported which limits understanding of the disease [3].

The Case for Bioelectrical Impedance Phase Angle

For over 30 years, bioelectrical impedance analysis (BIA) has been a method that has been used to estimate the body composition of patients both healthy and unhealthy. Similar to other body composition methods, bioimpedance devices do not directly measure body composition. Instead, they provide indirect estimates from the measurement of resistance of body tissues to an electric current [38]. BIA is a useful tool as it is non-invasive, relatively inexpensive, can be performed on nearly any patient as it is portable, does not expose the patient to ionizing radiation, is painless, and has both high intra- and inter-observer precision (coefficient of variation=2.7-4.0%) [39] [40, 41]. Measurements are taken by placing 2 electrodes on the hand and 2 on the foot from the same side of the patient. A small voltage, with fixed frequency of 50 Hz, is applied between the electrodes and the timing of the induced current is measured. The basis of BIA is the conductance of an alternating electrical current through body fluids and the fact that factors within the body impede the electrical current along the way. The body's impedance to the electric current comes from two sources: resistance (R, resistance offered by extra- and intracellular fluid) and capacitance or reactance (X_c, resistance offered by cell membranes) [42]. More specifically, resistance is determined by total body water (TBW=intracellular fluid (ICF)+extracellular fluid (ECF)) and reactance is determined by the body's proteins, bone minerals, and fat mass (Figure 1). Phase angle (PhA), a raw BIA variable, reflects the contributions of these two variables: (Xc/R) x 180/π [43, 44]. From a molecular perspective, PhA is an indicator of cellular health, specifically the electrical integrity of vital cell membranes, and the distribution of water between intracellular and extracellular spaces [45] [46]. Higher PhA values suggest large quantities of intact cell membranes and better cell function while, conversely, lower PhA values denote cell death and decreased cell integrity [43]. PhA is positively and significantly correlated with lean body mass and body cell mass (BCM) and inversely correlated to the extracellular to intracellular fluid ratio (ECW/ICW) in healthy

adults[47]. As disease-related malnutrition is classically characterized by an early shift of fluids from ICW to ECW, leading to an increased ECW/ICW, and decreased BCM, malnutrition has been shown to be negatively associated with PhA [48].

Figure 1 Resistance and Reactance of Bioimpedance Phase Angle and Their Body Composition Correlates. *Grundman et al., European Journal of Clinical Nutrition, 2015* [49]



Determinants of Phase Angle

The main determinants of PhA values are age, sex, body mass index (BMI), malnutrition, and inflammation. BMI, sex, and age's effects on PhA values have been extensively studied in healthy patients and all contribute via variables effects on cell mass and cell membrane integrity. PhA decreases with age due to decreases in muscle mass and a declining proportion of body water at the expense of increased fat mass. Women have lower PhA values due to decreased amount of muscle mass compared to men. As for BMI, higher BMI correlates with increased number of muscle and fat cells which leads to higher PhA values [50] [51] [41]. PhA is often lower in disease states due to influences such as malnutrition and inflammation. In a large cross-sectional study of hospitalized patients with the aim to explore determinants of PhA values, inflammation (assessed by C-Reactive Protein, CRP) and malnutrition (assessed by subjective

global assessment, SGA) were independent predictors of standardized phase angle. As will be discussed further below, standardized phase angle is a Z-score for patient's individual deviation of sex-, age- and BMI stratified mean reference values in order to remove the effects of those variables on the phase angle value and only represent the effect of a patient's disease on the measurement[52]. Further studies have shown, in disease-related malnutrition, increased ECW/ICW and decreased BCM are both reflected in the PhA [53] [54]. Furthermore, studies in various types of malignancies have all shown a gradual decrease in PhA with worsening malnutrition determined by SGA or patient generated subjective global assessment (PG-SGA) [48] [55]. For example, in a study conducted by Gupta et al, in 73 patients with advanced (stage III and IV) colon cancer, overall fair agreement was found between PhA and SGA [56]. Another study of 137 colorectal and gastric cancer patients, separated into two groups (currently being treated or having finished treatment), with the aim of comparing various objective and subjective assessment tools with regards to how well they correlated with SGA, showed PhA had the best association in terms of sensitivity with the SGA [55].

PhA has also been studied and suggested as an indicator of functional status. In a prospective study of 399 cancer patients (majority gastrointestinal, head and neck, and lung tumors), Norman et al found patients with PhA less than the 5th percentile, had significantly lower handgrip strength, peak expiratory flow, and KPS score ($P<0.0001$) [47]. In a study of Non-Small Cell Lung Cancer(NSCLC) patients by Castanho et al a positive correlation of PhA and KPS score was found ($r=0.44$; $P<0.05$) [57]. Another study examining the association between PhA and functional and nutritional status in 112 older adult nursing home residents found a significant correlation between PhA and hand grip strength, knee extension strength, and ADLs ($r= 0.411$, 0.373, and 0.395, respectively, $P<0.0001$) [58].

Phase Angle and Standardized Phase Angle: Prognostic Significance

Given that PhA is determined by and reflective of characteristics such as inflammation, malnutrition, and functional status, it is not surprising that PhA has been found to be prognostic in many diseases. It has been found to be prognostic for various endpoints, including mortality and disease progression, in several chronic conditions including HIV/AIDS, end stage renal disease on dialysis, and COPD [59] [45, 46] [60]. Additionally, PhA is prognostic for OS and 6 month mortality in many solid tumors, including breast, pancreatic, lung, colon, and hepatocellular carcinoma [61] [44, 57, 62-64]. In a study of 259 histologically confirmed breast cancer patients, after controlling for stage of tumor and prior treatment history, Gupta et al found decreased survival in those with PhA<5.6 ^{o} vs. >5.6 ^{o} (median survival 23.1 months; 95% CI: 12.2-31.9 vs. 49.9 months; 95% CI: 35.6-77.8, P=0.031) [61].The same group studied 165 patients with Stage IIIb or IV NSCLC and found similar results regarding median survival time, with patients with PhA<5.3^{o} vs. >5.3^{o} having median survival times of 7.6 months and 12.4 months, respectively, independent of cancer stage or prior treatment history [63]. In another study 119 treatment naïve NSCLC patients with ECOG PS 0-2 were prospectively studied to evaluate the association of PhA with survival. In multivariable analysis that included ECOG PS, sex, age, tumor stage, weight loss, SGA, and inflammatory markers, PhA, at a cut-off of 5.8^{o}, remained independently prognostic (HR, 3.02; 95% CI: 1.2-7.11; P=0.011) for OS [65].

As noted by Norman et al, the studies mentioned above generated PhA cut offs within their own study population by using the median or lowest quartile as the cut off value rather than a comparison of a healthy control. Furthermore, these cut offs do not consider determinants of PhA such as BMI and age, and thus values qualifying as “low PhA” could be due to low BMI or older age rather than disease specific determinants. In comparison, reference

values for PhA in the healthy population allow for assessing the individual deviation of a patient in relation to the population average and percentile for that given age, BMI, and sex. Similarly, reference values also allow for the calculation of standardized phase angle (SPhA), whereby a Z-score is calculated as follows: SPhA=(observed PhA-mean PhA/SD of PhA, where mean and SD are reference values. Of those reference values that have been published, only the health German population (n=214,732) are stratified by sex, age, and BMI [51] [43]. Utilizing those reference values, in a study of 399 mixed solid cancer patients, Norman et al demonstrated that the 5th PhA percentile is a prognostically relevant (ROC AUC=0.703 for survival) cut off and was predictive of increased 6-month mortality (OR=4.0; 95% CI 2.4-6.8; P<0.001). Paiva et al conducted a prospective observational cohort study to investigate the prognostic significance of the cut off of -1.65, which represents the 5th percentile as SPhA is a Z-score, in newly diagnosed, adult mixed cancer patients. In 195 patients, patients with SPhA<−1.65 had a lower survival rate than those with SPhA≥−1.65 (p<0.001). Furthermore, in unadjusted (HR 3.12 CI: 2.03–4.79; p<0.001) and adjusted (HR: 2.35 CI: 1.41-3.9 ;P=0.001) Cox regression the mortality rate was higher in patients with SPhA< −1.65 compared to SPhA≥−1.65. Models were adjusted for social class, race, site of primary tumor, tumor stage, age, and gender [66].

To date, no studies have been conducted examining the prognostic significance PhA with survival in leukemia patients of any age. However, two prospective studies, one in adults and one in children/adolescents, have been conducted in patients undergoing allogeneic hematopoietic stem cell transplant. In the adult population, Urbain et al conducted a prospective study of 105 patients, with hematological malignancies (76.2%: AML, MDS, ALL, chronic myeloid leukemia, and myeloproliferative disorders) as their indication for transplant, in order to analyze the prognostic significance of SPhA at a cut-off of -2.26 (25th percentile, Quartile 1 (Q1), of the SPhA in their study sample). In multivariate Cox regression including age

and gender-adjusted BMI (10th percentile), SPhA (≤-2.26), CRP (≥10 mg/dl), age (≥60), remission status (advanced disease), donor status (unrelated) KPS score (≤ 80), cytomegalovirus serology (+), and HLA-A,B,C, and DRB statuses (incompatible), only Q1 SPhA (HR=1.97; P=0.043), HLA-C incompatibility (HR=2.13; P=0.024), and unrelated donor (HR=2.64; P=0.039) were independently prognostic for 2 year OS. Furthermore, median survival time, relapse mortality, and progression-free survival all showed significant differences between the two SPhA categories. A notable limitation of this study was the utilization of their own determined cut-off value of 25th percentile rather than the previously suggested and validated 5th percentile of healthy German reference population. The authors note that their patients presented as extremely low SPhA values at admission, making the proposed cut off unusable. Thus, the external validity of this study is limited [66, 67].

In the pediatric population, a prospective study of 67 patients (majority (73%) non-malignant disease as indication for transplant) and 32 controls was conducted in children and adolescents (3-20 years) undergoing allogeneic hematopoietic stem cell transplant. In this study a SPhA cut off of 0 standard deviation was used as it showed a sensitivity and specificity of 92% and 70%, respectively, for detecting malnutrition based on World Health Organization expected weight for age[68]. There was a trend (P=0.054) toward lower SPhA in the transplant versus control group (Mean±SD: 0.61±0.98 and 1.0±0.6, respectively). In Kaplan-Meier survival analysis, patients with SPhA≤0 SD had shorter survival time (Mean survival=129.5 days; 95% CI 100.1-158.8) as compared to patients with SPhA>0 (Mean Survival=160.4 days; 95% CI 148.5-172.3) and increased risk of mortality (OR=5.163; 95% CI 1.41-18.94; p=0.013) [68].

Due to the limitations mentioned previously regarding patient and disease-specific prognostic factors in acute leukemia, particularly the time necessary for cytogenetic data to

become available, lack of sensitivity and tremendous subjectivity of PS scales, the large amount of uncategorized heterogeneity within the older adult population even in patients the same age, and the lack assessment of nutrition status by current geriatric assessment tools, a new tool to address these shortcomings would be beneficial. Given that PhA is painless, affordable, easily reproducible, strongly associated with nutrition and functional status, and validated as prognostic for survival in multiple malignancies and allogeneic-HSCT, a study to analyze the utility of this technology within the adult acute leukemia population is warranted. Accordingly, this prospective observational cohort study seeks to establish the feasibility and prognostic power of SPhA in acute leukemia patients undergoing intensive induction chemotherapy.

Specific Aims:

Primary Aim: To evaluate the association between standardized phase angle measured at the start of therapy and TRM (defined as 60-day mortality).

Primary Hypothesis: TRM is higher for patients with lower standardized phase angle measurements.

Secondary Aim #1: To evaluate the association of the day 14 standardized phase angle, as change in standardized phase angle, and outcomes including: length of hospitalization, transfer to intensive care unit during induction, treatment response (14-day bone marrow response, complete remission), and overall survival.

Secondary Hypothesis #1: Decline in standardized phase angle will be associated with increased length of hospitalization, increased transfer to ICU during induction, poor treatment response (poor 14-day bone marrow response and low complete remission), and decreased overall survival.

Secondary Aim #2: To document the feasibility of obtaining standardized phase angle measurements on patients hospitalized for treatment of newly diagnosed acute leukemia**.**

Secondary Hypothesis #2: Obtaining standardized phase angle measurements on patients hospitalized for treatment of newly diagnosed acute leukemia will be feasible.

Chapter 2:

The Prognostic Value of Standardized Phase Angle in Adults with Acute Leukemia: A Prospective Observational Study

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Abstract

We investigated the predictive value of standardized phase angle (SPhA) on 60-day mortality, overall survival (OS), and length of hospital stay (LHS) for adults with acute myelogenous and lymphoblastic leukemia (AML and ALL). Consecutive patients ≥18 years with newly diagnosed acute leukemia and receiving intensive chemotherapy were enrolled. Phase angle measurements were taken on day 1 of induction therapy for all patients and again on the day of nadir bone marrow for AML patients. Measurements were standardized by BMI, gender, and age to calculate the SPhA. The difference between SPhA at nadir bone marrow compared to day 1 of induction was used to calculate change in SPhA. A cut off of 25th percentile was used to dichotomize baseline SPhA. Cox proportional hazards models were fit for SPhA and change in SPhA as predictors of OS and LHS while logistic regression models were used to assess 60-day mortality. Among 100 patients 88% were AML, 56% were female, and mean age was 59 years. Though not statistically significant, OS by Kaplan-Meier analysis was shorter for those below the 25th percentile SPhA compared to those above (Median OS: 11.0 months vs. 19.5 months; P=0.09). Lower baseline SPhA was associated with increased incidence of 60-day mortality in univariable (OR=5.25; 1.35, 20.44; P=0.02) but not multivariable analysis (OR=3.12; 0.67, 14.48; P=0.15) adjusted for age, creatinine, and cytogenetics. Increased change in SPhA was associated

with worse OS (HR=1.15; 1.00-1.33; P=0.05) in multivariable analysis. SPhA is an objective measure that may be used to inform risk stratification.

Introduction

The acute leukemias in adulthood are comprised of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), a group of aggressive, molecularly heterogenous malignancies characterized by malignant, clonal proliferation of myeloid and lymphoid precursor cells, respectively. AML primarily affects older adults (≥60 years) with a median age at diagnosis of 67 years [(1)]. Due to its peak incidence at 1-4 years old, ALL is often perceived as a malignancy of children. However, there is another gradual increase in incidence in adults starting at 45 years of age and continuing into the older adult population [(1)]. Unlike in the pediatric population where intensive chemotherapy has produced cure rates approaching 90%, ALL in adults remains a tremendous challenge with 5-year survival rates for those 40-75+ years old between 9.1-38.9% [(2)] [(1, 3)]. The same can be said for AML in both the adult and older adult population where the 5-year survival rates for AML patients 40-64 years and ≥65 years are 37.9% and 7.1%, respectively [(1)]. Furthermore, due to the increased fear of treatment related mortality (TRM), there remains considerable disagreement on whether patients should receive intensive chemotherapy, or instead receive low intensity chemotherapy or best supportive care.

Much work has been done in the past decades to better discriminate between those patients who should receive intensive chemotherapy and those who are vulnerable to increased toxicity. Tumor-specific factors such as cytogenetics and gene mutations and patient-specific factors, primarily age and performance status, have been used to create prognostic scoring systems for TRM and overall survival (OS) [(8, 18, 21, 36)]. Each of these variables has their limitations.

Tumor-specific factors may take >1 week to become available [14] [6] [15]. Performance status scales lack sensitivity and are highly subjective [25] [27, 28]. Age is primarily a surrogate marker for impairments in nutritional status, cognitive function, physical function, and psychological state [25]. The complete geriatric assessment (CGA) has been used in ALL and AML patients in order to better characterize differences between patients of the same age [3, 28, 31, 33]. However, to this point no CGA tool incorporates nutritional status assessment, a known prognostic factor in AML and ALL patients of all ages [69-71] . Furthermore, no nutritional assessment tool (such as BMI, weight, or Subjective Global Assessment (SGA) questionnaires) or any of the various serum markers (albumin, pre-albumin, transthyretin) are consistently used in clinical practice [71].

Bioelectrical impedance analysis (BIA) is a method used to estimate body composition. BIA is a useful tool as it is non-invasive, relatively inexpensive, can be performed on nearly any patient, does not expose the patient to ionizing radiation, is painless, and has both high intra- and inter-observers precision (coefficient of variation=2.7-4.0%) [39] [40, 41]. Bioimpedance devices do not directly measure body composition but instead provide indirect estimates from the measurement of impedance of body tissues to an electric current [38]. The body's impedance to the electric current comes from two sources: resistance (R), determined by total body water, and reactance (X_c) determined by the body's proteins, bone minerals, and fat mass [42]. Phase angle (PhA), a raw BIA variable, reflects the contributions of these two variables: (Xc/R) x 180/π [43, 44]. From a molecular perspective, PhA is an indicator of cellular health, with higher PhA values suggesting better cell function while lower PhA values denote cell death and decreased cell integrity [43]. Phase angle is positively correlated with lean body mass and body cell mass and negatively correlated to the extracellular to intracellular fluid ratio (ECW/ICW) in healthy adults. As disease-related malnutrition is classically characterized by an increase ECW/ICW and decreased body cell mass, malnutrition (assessed by pre-albumin, albumin and malnutrition

questionnaires (SGA and NUTRIC)) has been shown to be negatively correlated with phase angle [48] [52] [43, 56, 72]. Due to the contributions of age, sex, and BMI to phase angle measurements, reference values were established and validated in order to calculate the standardized phase angle (SPhA), which controls for these variables. SPhA has proven to be a strong prognostic marker for various survival outcomes in numerous solid malignancies (lung, head and neck, pancreatic, breast, gastrointestinal) and transplant patients [67] [43] [52, 61, 63].

To date, no studies have evaluated the usage of phase angle technology in acute leukemia patients. This prospective observational study thus sought to establish the prognostic significance of baseline SPhA and change in SPhA for TRM and OS in newly diagnosed, adult ALL and AML patients receiving intensive chemotherapy.

Patients and Methods

Study population

Between July 2013 and January 2018 we conducted a single-institution prospective observational study where consecutive patients age ≥18 years who were newly diagnosed with pathologically confirmed AML or ALL were enrolled. Further were criteria included receipt of intensive (non-hypomethylating based) induction chemotherapy, inpatient status, and willing and able to provide written informed consent. Patients were excluded by presence of a pacemaker or defibrillator (due to possible interference of the bioimpedance analyzer with patient's defibrillator or pacemaker[40]), pregnant at time of enrollment, or any condition or abnormality which would, in the opinion of the investigator, compromise the safety of the patient. The treating physician at the time of diagnosis chose the treatment regimen before enrollment in the study and recording of phase angle measurements. This study was approved

by the Institutional Review Board of Wake Forest University Baptist Hospital. All participants provided written informed consent in accordance with the Declaration of Helsinki.

Study design and data collection

Standardized phase angle

We followed published procedures for PhA measurement collection [40]. Measurements were taken by placing 2 electrodes on the hand (ulnar head and first joint of third digit) and 2 on the foot (medial malleolus and base of second toe) on the same side of the patient, generally the right side. Participants were supine with their arms at a 30^{o} angle to their body and legs not touching each other or electrically conductive material of the inpatient bed. A single frequency (50 Hertz) alternating electrical current was then applied and reactance, capacitance, and PhA were recorded from the machine output. Bedside phase angle measurements were recorded (1) on first treatment day for all patients and (2), for AML patients, the same day as the nadir bone marrow (occurring on day 11-14 of induction therapy) on the inpatient ward by the study Physician Assistant. PhA values, in degrees(^{o}), were then used to calculate the SPhA (unit less) via the following equation: (SPhA)=(phase angle-phase $angle_{ref}$)/SD_{ref}, where SD_{ref} and phase $angle_{ref}$ are from the sex-,age-, and BMI-specific reference values from a healthy population [51]. Repeated measurements were always done on the same side as the first measurement. Height and weight were measured prior to each PhA measurement and were used to calculate body mass index (BMI). All measurements were taken using the Quantum IV bioelectrical impedance analyzer (RJL systems, Clinton Township, MI, USA). To dichotomize the SPhA we considered multiple cut offs: 25^{th} percentile (Q1) for our study (SPhA≤-0.948 vs. >-0.948), SPhA<-1.65 vs. ≥-1.65, and phase angle<5^{th} reference percentile (by age, BMI, and gender) vs. phase angle ≥5^{th}

reference percentile, based on previous reports[66] [47] [67]. The final cut off was chosen by which model had the lowest Akaike Information Criterion (AIC) for goodness of fit.

Covariates

Demographic (age, gender, race/ethnicity), laboratory data and comorbid conditions, assessed by the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI), at admission, and treatment data were collected from the electronic medical record. Tumor specific variables with prognostic significance were collected at baseline, including: lactate dehydrogenase level, white blood cell count, creatinine, and cytogenetic risk group from diagnostic bone marrow biopsy according to classification detailed by the Southwest Oncology Group [73] [24]. Of note, albumin and BUN values were collected at date of first and second PhA measurement rather than at admission.

Outcomes

The primary outcome of this study was 60-day mortality rate defined as the percent of patients no longer alive at 60 days after first phase angle measurement. A sample size of 102 was chosen as it would give 80% power to detect an odds ratio of 2.1, using a logistic regression model with a two-sided 0.05 alpha level and a 60-day mortality rate of 20%. Secondary outcomes included overall survival (OS), 30-day mortality rate, transfer to intensive care unit (ICU) during induction, nadir bone marrow response, complete remission (CR), and length of hospital stay. Overall survival was measured from date on study to either death or last follow-up in censored patients in accordance with 2010 ELN recommendations [6]. Nadir bone marrow response was defined as: hypoplastic marrow with <20% cellularity and <5% blasts. In our study the CR outcome included CR and CRi and was thus defined as: bone marrow blasts $<$ 5%, absence of blasts with Auer rods, lack of extramedullary disease, and independence of red cell

transfusions with or without the presence of blood cell count recovery (absolute neutrophil count > 1.0 x 10^9/L (1000/uL) platelet count > 100 x 10^9/L (100 000/uL))[6].

Statistical analyses

Means, standard deviations, and frequencies were used to describe baseline patient characteristics including demographics, comorbidity data, labs, cytogenetic risk group, and treatments. Proportions for response data were estimated for all patients. T-tests were used to assess differences in baseline patient characteristics and response rates across the two SPhA categories. To assess differences in categorical variables between the two SPhA groups, chi-square test and Fisher's exact test were used. Baseline SPhA was treated as a categorical measure. All outcomes were analyzed in univariable analysis and in adjusted models for the variables significant for TRM in the model by Kantarjian et al: age, creatinine, and cytogenetic risk group [21]. All categorical outcomes (60-day mortality, 30-day mortality, transfer to ICU, nadir bone marrow response, and CR) were modeled using logistic regression. Time-to-event analyses (OS and LHS) were conducted using the Kaplan-Meier method and Cox Proportional Hazards models (multivariable). Differences in Kaplan-Meier curves were assessed by log-rank test. For all analyses only complete data were analyzed. Interactions for age and SPhA were tested for all models and were included in the model if they fit the $P<0.05$ threshold. Subgroup analysis by age (≥60 years), gender, and leukemia type (AML) were conducted for all outcomes in unadjusted and adjusted models. All models were analyzed using change in SPhA (SPhA at nadir bone marrow-SPhA at day 1 of induction treatment). In an exploratory analysis, Pearson correlations were used to assess the association between change in SPhA and continuous determinants of the value (change in BUN, change in albumin, change in weight). Finally, multiple linear regression was used to assess predictors (change BUN, change albumin, change

in weight, and nadir marrow response) of change in SPhA. Cox regression was used to model the change in albumin with overall survival in an unadjusted model. For Cox Proportional Hazards models the proportionality assumption was assessed and met by visualization of the graph of each covariate predicting the outcome for categorical variables and the plotting of Schoenfeld Residuals for continuous variables. For logistic regression models the linearity assumption for continuous variables was assessed by the Hosmer-Lemeshow test and was met. SAS 9.4 software (SAS institute Inc., Cary, NC, USA) was used for statistical analysis using a two-sided α-level of 0.05.

Results

Participants:

One hundred two patients were consented, received PhA measurement at baseline, and completed follow up. 100 patients, 88 AML and 12 ALL, were included in the analysis. One patient was excluded due to not receiving intensive chemotherapy and the other due to having an outlier SPhA measurement (SPhA>15). Sixty-nine of the 85 (81%) patients eligible for second PhA measurement underwent the measurement. Most common reasons for those who did not receive second PhA measurement included interference of measurement due to machines present in ICU (n=3) and *C. difficile* infection (n=4). For full list of missing data please see the Supplementary Materials (Table 1). In addition, two cytogenetic test results were missing.

Descriptive data:

Of the 100 patients, 88 were AML, mean age was 59 (SD 14.6) years, and 56% were female (Table 1). Mean laboratory values indicated anemia, high levels of lactate

dehydrogenase, leukocytosis, and hypoalbuminemia. Only 4% had favorable cytogenetic abnormalities. 35% of the cohort showed significant comorbidity burden (HCT-CI≥3) at diagnosis. For those with AML, 80% received standard induction therapy with anthracycline and cytarabine (7+3) or alternative anthracycline and cytarabine-based induction regimens. All but two patients with ALL received the regimen per CALGB 10102 (ClinicalTrials.gov Identifier: NCT00061945). Between the two SPhA groups there were significant differences found between mean age and albumin (Table 1). SPhA means and SDs at baseline, nadir bone marrow, and change in SPhA measurements were 0.36 (1.99), 0.03 (2.21), and -0.05 (2.04), respectively (Table 2).

Of the 16 patients who did not receive a second PhA measurement, 9 of those were due to reasons where the patients were particularly ill (ICU machines leading to interference with measurement (3), patient with C. difficile infection (4), study team felt it inappropriate to gather measurement while patient was contemplating hospice after their nadir bone marrow showed poor response (2) (Supplemental Table 1).

Outcomes data:

Outcome data for complete remission, nadir marrow response, 30- and 60-day mortality, and requirement of ICU stay by overall cohort and AML subgroup are shown in Table 3. SphA was used in a categorical form using the cut-off of 25th percentile (-0.948) due to it having the lowest AIC (529.37) compared to SPhA=-1.65 (AIC=531.48) and phase angle<5th reference percentile (by age, BMI, and gender) (AIC=530.80) Statistically significant differences between the SPhA groups were seen in the proportion of patients dying within 60-days both in the overall cohort and in the AML subgroup, but only the overall cohort difference was significant (P=0.02 and P=0.06, respectively).

Analyses for baseline SPhA in the overall cohort and AML subgroup are shown in Table 4. SPhA was associated with 60-day mortality in the overall cohort and AML subgroup, though significance was only found in univariable analysis for the overall cohort (Table 4). Specifically, when controlling for age, cytogenetics risk group, and creatinine, those with SPhA≤-0.948 compared with those with SPhA>-0.948 had 3.12 times the odds of death within 60 days of start of induction (P=0.15). Median OS was lower in the lowest SPhA groups (SPHA <=-0.948: Median OS=11.0 months vs. SPHA>-0.948: Median OS=19.5 months; HR=1.57; 95% CI: 0.93, 2.66; P=0.09 (Figure 1), though the difference was not statistically significant. Similar results were found in the AML subgroup analysis (Figure 2). No association was found between baseline SPhA and logistic models for requirement of ICU stay, achievement of complete remission, and nadir marrow response. These analyses, along with subgroup analyses by gender and age≥60 years can be found in the Supplementary Materials (Table 2 and 3).

Change in SPhA was significantly associated with OS but not LHS and 60-day mortality. Specifically, when adjusted for cytogenetic risk group, age, and creatinine, for every 1-unit increase in standardized phase angle from day 1 of induction to nadir bone marrow there was an associated 15% increased risk of death during the two-year follow up period (HR=1.15; 1.00-1.33 P=0.05) (Table 5). Analyses for change in SPhA for ICU stay, achievement of complete remission, and nadir marrow response can be found in Supplementary Materials (Supplementary Table 4).

In exploratory analyses (Table 6), change in albumin and nadir marrow response were the strongest predictors of change in SPhA. Specifically, change in albumin was positively correlated (r=0.2, P=0.1) with change in SPhA and associated with a 0.75-unit increase in change SPhA per 1 g/dL increase in albumin when adjusted for change in BUN, weight, and nadir marrow response. In those who did not respond on nadir marrow, compared to those who did

respond, there was an associated 0.82-unit increase in change SPhA in the adjusted model (P=0.1). Furthermore, though not significant, for every 1g/dL increase in albumin from day 1 of induction to nadir bone marrow there was a 25% decreased risk of death within the 2 year follow up period (HR=0.75; 95% CI: 0.40, 1.40; P=0.37).

Discussion

To the best of our knowledge, this study is the first to assess and establish the prognostic significance of PhA technology in newly diagnosed adults with acute leukemia undergoing intensive chemotherapy. In our cohort we found differences in 60-day mortality by whether individuals were in the lower 25th percentile of baseline SPhA in our population compared those who were quartiles 2,3, and 4, though this association was significant only in univariable analysis. We also found change in SPhA to be a significant predictor of overall survival even when adjusted for age, cytogenetic risk group, and creatinine.

Our study adds to the growing body of literature showing the prognostic significance of SPhA in oncology and hematopoietic stem cell transplant (HSCT) patients [43, 67]. For example, in a study of 195 newly diagnosed mixed cancer patients, Paiva et al found the mortality rate was higher in patients with baseline SPhA< −1.65 compared to SPhA≥−1.65 [66]. Urbain et al conducted a prospective study of 105 HSCT patients, with hematological malignancies (76.2%: AML, MDS, ALL, CML, MPS) as their indication for transplant. In multivariable Cox regression including age and gender-adjusted BMI (10th percentile), SPhA (≤-2.26), CRP (≥10 mg/dl), age (≥60 years), remission status (advanced disease), donor status (unrelated), KPS score (≤ 80), CMV serology (+), HLA-A,B,C, and DRB statuses (incompatible), they found only SPhA (HR=1.97; P=0.043), HLA-C incompatibility (HR=2.13; P=0.024), and unrelated donor (HR=2.64; P=0.039)

were independently prognostic for 2 year OS. Furthermore, median OS, relapse mortality, and progression-free survival all showed significant differences between the two SPhA categories [67].

The values of SPhA at diagnosis in our study are higher than those found in previous literature utilizing SPhA in an oncology setting. Pena et al, in a study of adult mixed solid tumor patients scheduled to undergo surgical treatment, found a mean (SD) of -0.87+/-1.43 and 28.1% of their population to be SphA<-1.65 [74]. Similarly, in a study of mixed solid tumor patients about to undergo radiation therapy 27% of patients presented with SPhA<-1.65 [75]. Finally, in the study mentioned previously by Urbain et al they found a mean (SD) of -1.31+/-1.25 and 25th percentile=-2.26.

Our pilot study found a significant association in univariable but not multivariable logistic regression between our primary outcome, 60-day mortality, and baseline SPhA. However, our multivariable result neared significance (P=0.15) and had an effect size that was clinically relevant (OR=3.12) (Table III). Furthermore, our study was underpowered due to only 10 deaths occurring compared to the expected 20. Thus, we expect a follow up study with increased sample size would show a statistically significant result.

Our study is also the first to assess the prognostic significance of change in SPhA for mortality outcomes in oncology patients. In our study we found change in SPhA to be a significant predictor of mortality with an increase in SPhA from day 1 of induction to nadir bone marrow predicting increased mortality in AML patients. Due to direction of the association being the opposite of baseline SPhA, where higher values are associated with better prognosis, the exploratory analysis to assess predictors of change SPhA was conducted. Though no predictors were statistically significant, nadir marrow response and change in albumin showed the strongest effects. In those who did not respond on nadir bone marrow, compared to those who

did respond, there was a 0.82-unit increase in change in SPhA when controlling for change in BUN, change in albumin, and change in weight. Similarly, for every 1 g/dL increase in albumin from day 1 of induction to nadir bone marrow there was a 0.75-unit increase in change SPhA when controlling for change in BUN, change in weight, and nadir marrow response. Furthermore, though not significant, for every 1g/dL increase in albumin from day 1 of induction to nadir bone marrow there was a 25% decreased risk of death within the 2 year follow up period (HR=0.75; 95% CI: 0.40, 1.40; P=0.37). From these exploratory analyses we cautiously conclude the direction of the change in SPhA effect on OS is due to representing response to chemotherapy during induction. However, change in patient's nutrition status, as assessed by albumin, appears to also be represented by the measure. There are notable limitations to our interpretations regarding change in SPhA. First, whether phase angle technology has the ability to assess the burden of leukemia in patient's bone marrow is not known. Furthermore, change in SPhA did not predict CR status in univariable or multivariable analysis which would have been expected if the change in SPhA value was a surrogate marker for marrow response as the predictive ability of nadir marrow response for CR is well-documented [(4)]. Future studies need to be conducted to specifically assess the question of content validity of change in SPhA.

A limitation of our study is the utilization of the lower quartile (25th percentile) SPhA, reducing the external validity of our results, rather than a previously published, validated cut off value. However, this cut off has been shown to be prognostically relevant [(67)] and was chosen by a validated goodness-of-fit criteria (AIC) in comparison to those cut offs in previous studies [(47, 66)]. A further limitation includes the lack of collection of performance status and inflammation parameters. Another limitation to consider in our results concerns selection bias in the change in SPhA results. This bias may have shifted our HR and OR estimates towards or away from the null hypothesis of no association between change in SPhA and outcome but we are unable to

further infer on the effect of the bias. Lastly, a limitation of PhA technology is a lack of an exact understanding of the physiologic meaning of PhA. Though many authors claim that phase angle is validated as a nutritional status marker[43], in a recent review focused on assessing the association between PhA and malnutrition in adults, Lukaski et al stated that though many studies find a correlation between PhA and measures of nutritional status low PhA cannot specifically reflect impaired nutritional status, particularly in patients with inflammatory processes where the associated overhydration may lower PhA more than explained by their nutritional status. If a better understanding of the content validity of PhA could be had it would allow for stronger evidence to pursue interventions based on the information provided by the measure. Specifically, promising work has been done to determine the effects of interventions, chiefly resistance training and nutritional support, to minimize sarcopenia and increase muscle function in patients with low PhA [76] [77, 78].

In conclusion, our findings suggest that in newly diagnosed acute leukemia patients undergoing intensive induction chemotherapy standardized phase angle technology may provide important prognostic information for TRM and OS. PhA is an objective, repeatable, high precision measure in acute leukemia patients and, unlike other prognostic factors in this population, is theoretically intervenable. Future studies of PhA technology in leukemia patients should address the content validity of phase angle while further exploring the promising findings of the effect of strength training and nutritional supplementation on PhA and patient outcomes.

Table 1. Patient Characteristics at Baseline

	All patients (n=100), Mean+/-SD, or N (%)	Standardized Phase Angle: Quartile 1 (≤-0.948°) (n=26), Mean+/-SD, or N (%)	Standardized Phase Angle: Quartiles 2,3,4 (>-0.948°) (n=74) Mean+/-SD, or N (%)	*P*[A]
Diagnosis				0.730
AML	88 (88.0%)	24 (92.3%)	64 (86.5%)	
ALL	12 (12.0%)	2 (7.7%)	10 (13.5%)	
Age	58.9+/-14.6	65.5+/-12.1	56.6+/-14.6	0.007
<60 years	43 (43.0%)	7 (26.9%)	36 (48.7%)	0.054
≥60 years	57 (57.0%)	19 (73.1%)	38 (51.4%)	
Gender (Female)	56 (56.0%)	15 (57.7%)	41 (55.4%)	0.840
Race (white)	89 (89.0%)	24 (92.3%)	65 (87.8%)	0.724
BMI	29.7+/-7.1	27.4+/-7.3	30.6+/-6.9	0.052
Labs				
Hemoglobin (g/dL)	9.3+/-2.0	9.1+/-2.0	9.4+/-2.1	0.500
LDH (U/L)	533.2+/-681.3	467.2+/-454.1	556.3+/-746.1	0.476
White Cell Count (10^9/L)	31.2+/-62.5	40.6+/-58.4	27.8+/-63.9	0.374
Creatinine (mg/dL)	1.03+/-0.47	1.08+/-0.41	1.01+/-0.50	0.495
BUN (mg/dL)[B]	15.9+/-8.5	15.6+/-8.0	16.0+/-8.7	0.840
Albumin (g/dL)[B]	3.3+/-0.5	3.1+/-0.5	3.4+/-0.4	0.014
Cytogenetic Risk Group[C]:				0.772
Favorable	4 (4.1%)	0 (0.0%)	4 (5.4%)	
Intermediate	54 (55.1%)	14 (58.3%)	40 (54.1%)	
Unfavorable	40 (40.8%)	10 (41.7%)	30 (40.5%)	
HCT-CI≥3	35 (35%)	9 (34.6%)	26 (35.1%)	0.960

Induction Therapy				0.820
AraC+Anthracycline	64 (64.0%)	15 (57.7%)	49 (66.2%)	
As per CALGB 10102	10 (10.0%)	2 (7.7%)	8 (10.8%)	
AraC+Anthracycline and Rydapt	4 (4.0%)	1 (3.8%)	3 (4.1%)	
AraC+Anthracycline and HiDAC/Mitox	2 (2.0%)	0 (0%)	2 (2.7%)	
Clofarabine	8 (8.0%)	4 (15.4%)	4 (5.4%)	
Other	12 (12.0%)	4 (15.4%)	8 (10.8%)	

[A]Calculated using Chi-square test or Fisher's exact test (if expected n<5 in any cell of the contingency table) for categorical variables and t-tests for continuous variables.

[B]N=98

[C]N=98; Cytogenetic test results were unavailable for 2 subjects. Favorable and intermediate were combined to form a single variable for significance testing compared to unfavorable due to the lack of patients with favorable cytogenetics.

Table 2 Baseline, Nadir Bone Marrow, and Change in Phase Angle Measurements

Baseline in Total Population (n=100)	Mean +/-SD	Min, 5^{th}, 25^{th}, 50^{th}, 75^{th}, 95^{th} Max
Phase Angle $^{(o)}$	6.07+/-1.67	2.60, 3.70, 5.00, 5.90, 7.20, 9.55, 10.20
Standardized Phase Angle	0.36+/-1.99	-3.26, -2.37, -0.95, 0.02, 1.53, 4.49, 5.62
Baseline for those who received Nadir Marrow (n=68)		
Phase Angle $^{(o)}$	5.84+/-1.44	3.10, 3.80, 4.95, 5.70, 6.75, 8.40 9.60
Standardized Phase Angle	0.08+/-1.72	-3.26, -2.19, -0.95, -0.30, 1.08, 3.01, 4.46
Standardized Phase Angle at Nadir Bone Marrow (n=68)		
Phase Angle $^{(o)}$	5.83+/-1.74	2.40, 3.30, 4.70, 5.50, 6.75, 8.90, 10.80
Standardized Phase Angle	0.03+/-2.21	-4.11, -2.89, -1.55, -0.30, 1.12, 4.08 6.28
Change in Standardized Phase Angle (n=68)	-0.05+/-2.04	-4.14,-3.03, -1.03, -0.25, 0.66, 4.35, 8.16

Table 3. Outcome Data

Response*	All patients (n=100) A	Standardized Phase angle: ≤-0.948° (n=26)	Standardized Phase Angle: >-0.948° (n=74)	*P* μ	Diagnosis: AML (n=88)	Standardized Phase angle: ≤-0.948° *(n=24)*	Standardized Phase Angle: >-0.948° *(n=64)*	*P* μ
Complete Remission Achieved	80 (80.0%)	19 (73.1%)	61 (82.4%)	0.3	69 (78.4%)	18 (75.0%)	51 (79.7%)	0.63
14-Day Marrow Response	46 (53.5%)	13 (56.5%)	33 (52.4%)	0.73	46 (53.5%)	13 (56.5%)	33 (52.4%)	0.73
30-day mortality	6 (6.0%)	3 (11.5%)	3 (4.1%)	0.18	5 (5.7%)	2 (8.3%)	3 (4.7%)	0.61
60-day mortality	10 (10.0%)	6 (23.1%)	4 (5.4%)	0.02	9 (10.2%)	5 (20.8%)	4 (6.3%)	0.06
Required ICU Stay	10 (10.0%)	5 (19.2%)	5 (6.8%)	0.12	9 (10.2%)	4 (16.7%)	5 (7.8%)	0.25

[A]14-Day Marrow Response results were not recorded for ALL patients and were missing in 2 AML patients. N=23 and N=63 for ≤-0.948° and > -0.948°, respectively.

*All response for event YES.

μ Analyses conducted using Chi-Square or Fisher's Exact Test.

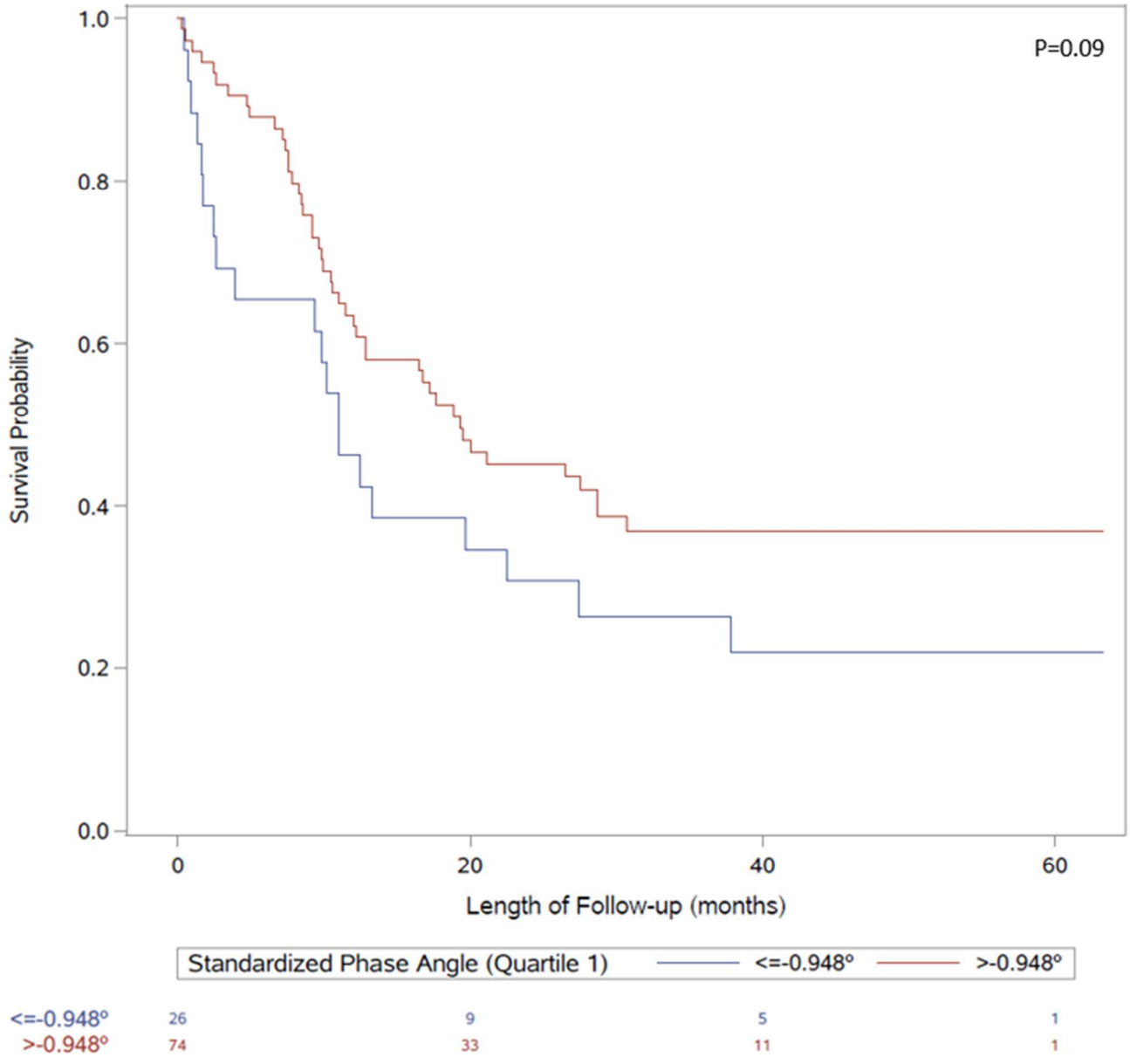

Figure 1. Survival by Log-Rank test of 100 AML and ALL patients by standardized phase angle.

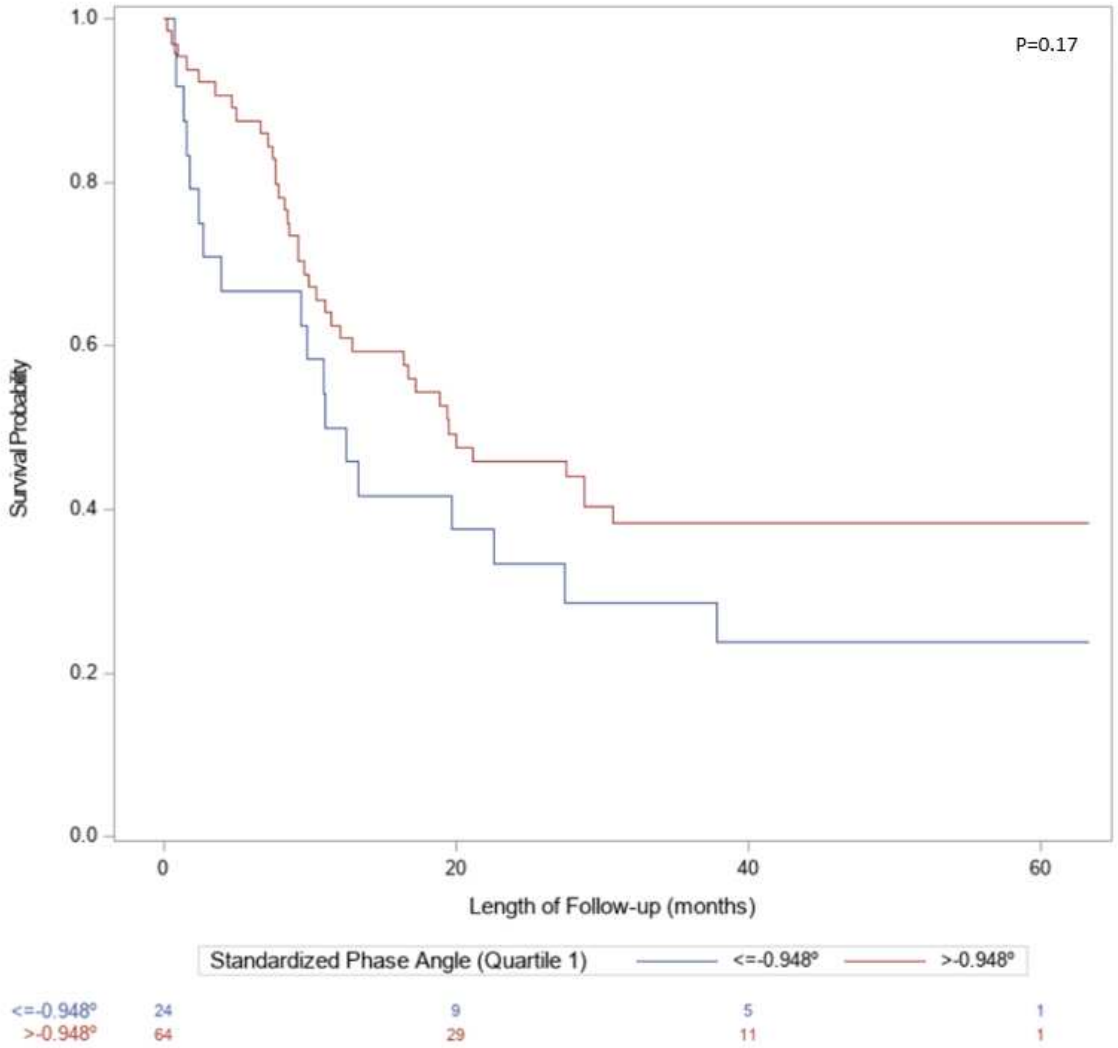

Figure 2. Survival by Log-Rank Test of 88 AML patients by standardized phase angle.

Table 4 Models for 60-day mortality, Overall Survival, and Length of Hospital Stay by Baseline Standardized Phase Angle as Predictor.[Σ]

	Hazard Ratio (95% CI)		
Model		Overall Unadjusted (n=100) Adjusted (n=98)	AML Unadjusted (n=88) Adjusted (n=87)
Overall Survival	SPhA (Unadjusted)	1.57 (0.93, 2.66) P=0.09	1.46 (0.84, 2.55) P=0.17

	SPhA (Adjusted)[b]	1.23 (0.71, 2.15) P=0.46	1.24 (0.69, 2.23) P=0.46
Length of Hospital Stay	SPhA (Unadjusted)	0.86 (0.53, 1.38) P=0.52	0.89 (0.55, 1.46) p=0.64
	SPhA (Adjusted)[b]	0.95 (0.57, 1.57) p=0.84	0.94 (0.56, 1.61) p=0.83
Odds Ratio (95% CI)			
60-day Mortality	SPhA (Unadjusted)	5.25 (1.35, 20.44) P=0.02	3.95 (0.96, 16.21) P=0.06
	SPhA (Adjusted)[b]	3.12 (0.67, 14.48) P=0.15	3.17 (0.66. 15.21) P=0.15

[b]Adjusted for age, cytogenetic risk group, and creatinine as per Kantarjian study. Performance status data was not collected for this study and thus is not included in the model.

[Σ]All estimates are for low standardized phase angle compared to normal phase angle using cut off of Q1 in our cohort (SPhA <=-0.948^{o} vs. SPhA>-0.948^{o}).

Table 5 Models for 60-day mortality, Overall Survival, and Length of Hospital Stay by Change in Standardized Phase Angle (ChangeSPhA) as predictor.

Hazard Ratio (95% CI)		
Model		Overall Unadjusted (n=68) Adjusted (n=67)
Overall Survival	Change in SPhA (Unadjusted)	1.15 (1.01, 1.31) P=0.03
	Change in SPhA (Adjusted)[b]	1.15 (1.00, 1.33) P=0.05
Length of Hospital Stay	Change in SPhA (Unadjusted)	0.99 (0.85, 1.14) P=0.83
	Change in SPhA (Adjusted)[b]	0.97 (0.83, 1.13) P=0.69
Odds Ratio (95% CI)		
60-day Mortality	Change in SPhA (Unadjusted)	1.26 (0.86, 1.85) P=0.23
	Change in SPhA (Adjusted)[b]	1.18 (0.75, 1.85) P=0.47

[b]Adjusted for age, cytogenetic risk group, and creatinine as per Kantarjian study. Performance status data was not collected for this study and thus is not included in the model.

Table 6 Pearson correlation and multiple linear regression results for determinants of change in standardized phase angle.

Predictor	Correlation Coefficient (r)	P-value	Coefficient for Multiple Linear Regression*	P-value
Δ BUN	-0.11	0.37	-0.02	0.43
Δ Weight	-0.09	0.47	-0.001	0.97
Δ Albumin	0.20	0.10	0.75	0.20
14-Day Marrow Response (No)**	N/A	N/A	0.82	0.10

*Each variable adjusted for other variables listed in Table 6.

**Estimate compares those who did not respond (No) to their 14-day marrow to those who did (Yes) respond.

Chapter 3:

Feasibility Analysis Results

Feasibility analysis results assessing accrual rate and proportion of individuals able to undergo a phase angle measurement at baseline and at the nadir bone marrow are shown in Table VII. All patients consented (n=102) were included in the denominator for the outcome of proportion of patients receiving baseline phase angle measurement. For the outcome of proportion of patients who recorded phase angle measurement at nadir marrow, individuals were excluded from the analysis if they were not scheduled to have a nadir bone marrow (ALL patients and patients deceased before the nadir marrow) or if circumstances dictated moving their nadir bone marrow to a point where the phase angle measurement would no longer contribute to analyses. The later reason occurred in the case of one patient who received treatment with Clofaribine, where nadir marrows are done at day 21, and one patient who was deemed too ill to receive the nadir marrow until day 19. Overall, a total of 85 patients contributed to the second phase angle feasibility analysis with 69 of them receiving a second phase angle measurement. Finally, accrual rate was defined as the number of patients who agreed to participate divided by the number of months of recruitment.

Table 7. Feasibility Analyses

	Point Estimate and 95% Confidence Interval
Proportion of patients who recorded Phase Angle measurement at Baseline	**1.00 (0.9645,1.00)***
Proportion of Patients who recorded Phase Angle measurement at Nadir Bone Marrow.	**0.81 (0.73, 0.89)***
Accrual Rate (participants/month)	**1.88 (0.21, 7.03)****

*Exact 95% CI for Proportion.

**Exact 95% CI for Poisson mean.

Patient-Specific Factors Prognostic Factors: Nutrition Status

To this point no assessment tool or laboratory test has been accepted as the gold standard for nutritional status evaluation in leukemia patients. BMI, weight, questionnaires (SGA and PG-SGA), and various serum markers (albumin, pre-albumin, transthyretin) have been used [69] [79, 80] [81]. Despite inconsistency regarding the tool used to assess nutrition status, knowledge regarding the significance of nutrition status in the evaluation of acute leukemia patients can be gained from these studies. Worse nutritional status has been associated with increased LHS [69] [79], worse quality of life [82], increased duration of neutropenic fever (DNF) [79], decreased treatment effectiveness, and increased vulnerability to side effects of chemotherapy. Nutritional status has proven prognostic for survival in multiple studies [69-71]. Using BMI and weight in order to categorize AML patients as underweight, defined by a weight loss >5%, and/or a BMI (but not used alone) <18.5 kg/m2 or 21 kg/m^2 for patients ages ≥70, Deluche et al found survival rates at 12 months to be significantly higher for patients without undernutrition at diagnosis (89.9%) compared to those with undernutrition (53.8%) (P=0.002) [69]. Similarly, Li et al. found PG-SGA, where they compared severely (PG-SGA≥9) vs. non-severely (PG-SGA<9) malnourished AML and ALL patients at time of diagnosis, to be significant for OS in multivariable analysis using Cox Hazard models adjusting for remission status, cytogenetics, and WBC at baseline (HR=0.243, 95% confidence interval [CI]: 0.063– 0.945, P=.041) [70]. Finally, Filliatre-Clement et al found albumin (≥30 vs. <30) (HR=0.467, 95% CI: 0.230-0.946; *P*=.03) to be a significant predictor of OS when controlling for age (≥60 years vs. <60 years), ELN cytogenetic group, and FLT3 mutation status [71].

Two key clinical principles have been learned from these studies analyzing the importance of nutrition status in acute leukemia. For one, in acute leukemia, unlike other

malignancies, malnutrition at diagnosis is found much less commonly. Second, nutrition status then quickly declines within weeks of treatment. For example, multiple studies have found newly diagnosed acute leukemia patients to present with normal BMI, minimal weight loss, and malnutrition at lower rates than other malignancies that then rapidly declines during induction [69] [82]. Malihi et al found a large decrease in nutrition status by PG-SGA (19.4% patients malnourished at diagnosis with none being severely malnourished, whereas 76.1% were moderately malnourished and 15.97% were severely malnourished) from baseline to 21 days into treatment [82]. Similarly, a retrospective study of newly diagnosed AML and ALL patients analyzing nutrition status at diagnosis and through induction found nutrition status variables assessed at day 21 of treatment to be more consistently correlated with DNF and LHS in both AML and ALL patients compared to those assessed at baseline [79]. The relatively low incidence of malnutrition at baseline is thought to be due to the sudden onset of acute leukemia while the rapid decline is due to the side effects of AML regimens such as stomatitis, diarrhea, anorexia, and depression [83]. Two retrospective studies assessed the hypothesis that the amount of food and variety of food intake changed throughout induction, theoretically due to side effects of medications, and that those values correlated with nutrition status [69] [80]. The results of these studies were inconclusive.

There are several limitations to these studies. All studies were retrospective or cross-sectional in nature. These studies also do not have a representative AML patient population as the samples are much younger than the median age of AML (67 years), with the exception of the study by Deluche et al (Median=58 years) [69]. Furthermore, most of the analyses for survival and response outcomes have been done only in univariate analyses, with only one study assessing nutrition status's prognostic significance in the context of other known variables with prognostic significance. Finally, each of the variables used to assess nutritional status have their own

limitations. For instance, weight loss due to malnutrition may be masked by over hydration to avoid tumor lysis syndrome or weight loss unrelated to malnutrition may occur due to frequent diuretic use [84]. Albumin, with a 20-day half-life, is not an accurate marker of effectiveness of nutrition management. Furthermore, albumin decreases with inflammation which is frequently present in acute leukemia [69]. Thus, Deluche et al, following with French guidelines, suggest only interpreting albumin in the presence of C-reactive protein (CRP) results [85]. Pre-albumin, with a 2-3 day half-life, is more appropriate for nutrition assessment in short intervals. However, like albumin, pre-albumin decreases during inflammation as it is used to synthesize CRP. Pre-albumin also increases in the presence of steroids, complicating its interpretation in ALL patients where steroids are commonly part of the chemotherapeutic regimen [86]. Transthyretin suffers from similar limitations as albumin and pre-albumin and is also more reflective of acute food intake rather than overall nutrition status. Finally, questionnaires such as the Subjective Global Assessment (SGA) and Patient-Generated Subjective Global Assessment (PG-SGA) are subjective tools which, while highly sensitive to symptoms and assess key factors such as metabolic stress and physical activity, only briefly assess possible food intake and thus may not be particularly sensitive to malnutrition in the first month of treatment when muscle-wasting is less likely [80] [87].

The Short Physical Performance Battery (SPPB)

The Short Physical Performance Battery (SPPB) is a validated measure of physical function in the geriatric population [88]. As mentioned previously, performance status scales lack sensitivity, are subjective, and do not address specific tasks. This was further demonstrated in a study by Klepin et al where older adults with "good" performance status scores were found to have meaningful impairments in physical function that may reduce reserve capacity and increase their susceptibility to TRM [26]. As a part of the battery of tests utilized in the complete geriatric assessment, SPPB is an objective tool to assess functional status by measuring lower extremity strength. Specifically, the SPPB consists of a timed 4 meter walk, chair stands, and balance testing for a score ranging from 0 (worst) to 12 (best) with each measure being scored 0 to 4 (0=unable to complete the test; 4=highest performance level) [88]. The SPPB has training modules publicly available online and the test can be performed in the inpatient setting by a trained nurse. The SPPB has already been shown to be feasible in an inpatient leukemia unit setting [26]. In older adult AML patients intensively treated a low (SPPB<9) score, when compared to those with better physical performance (SPPB≥9), has been shown to be predictive of OS (6.0 months vs. 16.8 months; P=0.018) and risk of mortality (HR 2.2; 95% CI 1.1-4.6) even when adjusted for age, gender, ECOG performance status, cytogenetic risk group, prior MDS, hemoglobin, and treatment type [31]. Furthermore, in exploratory analyses, though not significant, differences were seen in the proportion of individuals with TRM (defined as 30-day mortality in their study) by SPPB<9 (18.9%) vs. SPPB≥9 (10.8%) (P=0.5) [31]. Mechanisms by which impaired physical function lead to worse survival appear to be similar to those previously mentioned for impaired nutritional status.

Though not measured by the SPPB, two studies have assessed the association between physical function and SPhA in oncology patients. In a study of 121 mixed solid tumor patients scheduled to receive surgical treatment, Pena et al found patients with SPhA<-1.65 to have 3.84 times the odds of having muscle strength depletion assessed by hand grip strength compared to those SPhA≥-1.65 (OR=3.84; 95 CI: 1.31, 11.25; P=0.01) [74].. In a study of 399 mixed solid tumor patients, Norman et al found differences in hand grip strength by whether individuals were SPhA<-1.65 vs. SPhA≥-1.65 (P=0.01) and a moderate correlation between hand grip strength and SPhA (r=0.60; P=0.01) [47]. The authors of both these studies not, however, that further studies are needed to prove the association between physical function and SPhA

Future Directions

In our future work we hope to assess the current limitations of SPhA technology and nutritional status assessment in AML patients. Specifically, we plan to conduct a prospective observational study of newly diagnosed, older adult AML patients undergoing intensive induction chemotherapy with the following Specific Aims:

Specific Aim 1: Assess the prevalence of physical function impairment at day 1 of induction, as assessed by the SPPB, and malnutrition, via utilization of the patient-generated subjective global assessment, standardized phase angle, pre-albumin, and albumin, in newly diagnosed older adult (≥60 years) AML patients undergoing intensive induction chemotherapy both at day 1 of induction therapy and at nadir bone marrow (occurring between day 11-15 of induction chemotherapy). ***Hypothesis****:* 20-30% of patients will present with malnutrition, as defined by PG-SGA (PG-SGA≥9), albumin<3.4 g/dL, pre-albumin<16mg/dL, SPhA<25th percentile, at baseline and the percentage of patients classified as malnourished will increase from day 1 of induction to nadir bone marrow. 50-60% of patients will present with physical function impairments (SPPB<9) at diagnosis.

Specific Aim 2. Evaluate the prognostic value of SPPB assessed at day 1 of induction and nutritional assessment markers specified in Aim 1 at day 1 of induction and at nadir bone marrow for treatment related mortality, defined as death within 60 days of start of induction therapy. ***Hypothesis***: Nutritional assessment markers at **nadir bone marrow**, aside from SPhA, will predict treatment related mortality in the context of key covariates: age, European Leukemia Network cytogenetic risk group, creatinine, and performance status. SPhA at **day 1 of induction** will predict treatment related in the context of the covariates mentioned above.

Specific Aim 3: Assess the content validity of baseline SPhA via correlation with SPPB, nutritional status markers specified in Aim 1, and Computed Tomography assessed sarcopenia.

Hypothesis: Baseline SPhA will be best predicted by the PG-SGA with higher scores on the PG-SGA, reflecting worse nutritional status, predicting lower baseline SPhA values.

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Appendix

Manuscript Supplementary Materials

Table 1 Reasons for Non-compliance with Second Phase Angle Measurement.

Reason for Missed 2nd Phase Angle	Count (n=16)
Interference with measurement due to machine in ICU.	3
Patient declined	1
C. difficile infection (threat of contamination of phase angle device)	4
Patient had marrow poor response and study team felt it inappropriate to ask for measurement to be recorded while family and patient was contemplating hospice.	2
Data collector was on vacation.	1
Patient received pacemaker between first and second measurement which is a contraindication to taking measurement.	1
Reason not recorded	4

Table 2 Logistic Regression models for 60-day mortality, 30-day mortality, complete remission, 14-day marrow response, and requirement of ICU stay in overall cohort and subgroup analyses by age and gender. [Σ]

Odds Ratio (95% CI)[*]					
Model		Overall Unadjusted (n=100) Adjusted (n=98)	Age≥60 y N=56	Females N=55	Males N=43
60-Day Mortality	Unadjusted	5.25 (1.35, 20.40) P=0.02			
	Adjusted[b]	3.12 (0.67, 14.48) P=0.15	3.98 (0.78, 20.36) p=0.10	2.33 (0.24, 22.31) P=0.46	1.34 (0.01, 18.77) P=0.83
Complete Remission Achieved	Unadjusted	0.64 (0.21, 1.92) p=0.43			
	Adjusted[a]	0.81 (0.26, 2.57) P=0.72	0.48 (0.13, 1.78) P=0.27	0.4 (0.08, 2.00) P=0.26	N/A[#]
14-day Marrow Response Achieved[α]	Unadjusted	0.92 (0.35, 2.42) p=0.86			

	Adjusted[b]	0.92 (0.33, 2.58) p=0.88	0.45 (0.12, 1.72) P=0.24	0.25 (0.04, 1.66) P=0.15	2.5 (0.54, 11.20) P=0.24
Required ICU Stay	Unadjusted	2.76 (0.68, 11.26) p=0.16			
	Adjusted[b]	2.88 (0.64, 13.02) P=0.17	3.86 (0.55, 26.93) P=0.17	2.27 (0.22, 23.6) P=0.49	N/A[#]

[b]Adjusted for age, cytogenetics, and creatinine as per Kantarjian study. Performance status data was not collected for this study and thus is not included in the model.

[#]Model could not be fit due to Quasi-Complete separation.

[*]Odds ratio and 95% confidence interval for all outcomes was for event=YES.

[Σ]All estimates are for low standardized phase angle compared to normal phase angle using cut off of Q1 in our cohort (SPhA <=-0.948 vs. SPhA>-0.948).

[α]Number of observations for unadjusted (n=85), adjusted (n=84), age (n=49) subgroup analysis, male (n=40) subgroup analysis, and female (n=44) subgroup analysis.

Table 3. Cox proportional hazards models for overall survival (OS) and length of hospital stay (LHS) predicted by standardized phase angle (SPhA) in age, and gender subgroups. [Σ]

Hazard Ratio (95% CI)[*]			
Model	Age≥60 y N=56	Females N=55	Males N=43
Overall Survival	1.47 (0.78, 2.79) P=0.23	1.36 (0.63, 3.00) P=0.43	0.92 (0.38, 2.22) P=0.85
Length of Hospital Stay	0.78 (0.42, 1.43) p=0.42	0.77 (0.37, 1.59) p=0.47	1.36 (0.61, 3.05) P=0.30

[b]Adjusted for age, cytogenetics, and creatinine as per Kantarjian study. Performance status data was not collected for this study and thus is not included in the model.

*Modeling for Cox hazards models was for death (OS) and discharge (length of hospital stay).

[Σ]All estimates are for low standardized phase angle compared to normal phase angle using cut off of Q1 in our cohort (SPhA <=-0.948 vs. SPhA>-0.948).

Table 4 Models for complete remission, nadir marrow response, and requirement of ICU stay by Change in Standardized Phase Angle (Change in SPhA) as predictor.

Odds Ratio (95% CI)[*]		
Model		Overall

		Unadjusted (n=68) Adjusted (n=67)
Complete Remission Achieved	Change in SPhA (Unadjusted)	0.91 (0.67, 1.23) P=0.53
	Change in SPhA (Adjusted)[b]	0.90 (0.64, 1.26) P=0.54
14-Day Marrow Response Achieved	Change in SPhA (Unadjusted)	0.79 (0.60, 1.04) P=0.09
	Change in SPhA (Adjusted)[b]	0.80 (0.59, 1.07) P=0.13
Required ICU Stay	Change in SPhA (Unadjusted)	1.16 (0.80, 1.69) P=0.43
	Change in SPhA (Adjusted)[b]	1.12 (0.74, 1.69) P=0.61

[b]Adjusted for age, cytogenetic risk group, and creatinine as per Kantarjian study. Performance status data was not collected for this study and thus is not included in the model.

[*]Odds ratio and 95% confidence interval for all outcomes was for event=YES.

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EDUCATION

- **Wake Forest School of Medicine,** Doctor of Medicine (anticipated graduation date 5/2020) — 6/2015-Present
- **Wake Forest Graduate School of Arts and Sciences**, Master of Clinical and Population Translational Sciences (anticipated graduation date 8/2019) — 8/2018-Present
- **Mercer University,** Bachelor of Science, Biology — 8/2011-12/2014

CLINICAL RESEARCH

Wake Forest Department of Internal Medicine Section on Infectious Diseases — 5/2016-3/2018

Advisor: Katherine Schafer, MD

Study: ***The effects of religious involvement on HIV management outcomes among HIV-positive adults in central North Carolina: a pilot cross-sectional study.***

- Role: data gathering, manuscript production, and manuscript submission.
- Poster Presentation: Wake Forest Medical Student Research Symposium, 2016
- Peer-Reviewed Publication: Yates, T, **Yates, S**, Schafer, K, Rushing, K (2018) Southern Medical Journal.

Wake Forest Department of Internal Medicine Section on Hematology and Oncology — 6/2018-Present

Advisor: Timothy Pardee, MD

Study*: Investigating the prognostic importance of Bioelectrical Impedance Phase Angle in adults treated for newly diagnosed acute leukemia*

- Role: Co-Investigator: data gathering, literature review, manuscript production, and manuscript submission.

Wake Forest School of Medicine — 8/2017-Present

Advisor: Roy Strowd III, MD

Study*: Cultivating student connection and decreasing burnout through near-peer mentoring with a Student Guide Program.*

Role: Co-Investigator: data gathering and manuscript production.

Peer-Review Publication: Laurence C, Ykimoff J, Moses-Hampton M, **Yates S**, Callese TE, Keskinyan VK, Moses-Hampton M, Davis G, Wirth S, McNamara K, Husain I MD, Bentley PhD, Reynolds P MD, Strowd RE MD. IN SUBMISSION.

TEACHING EXPERIENCE

Organic Chemistry, Biochemistry and Genetics, Mercer University, Tutor and Teaching Assistant — 8/2012-12/2014

- Worked with undergraduate students one-on-one as well as large groups to aid in learning Biochemistry, Genetics, and Organic Chemistry.

Case Centered Learning, Wake Forest School of Medicine, Assistant Instructor — 8/2018

- Served as assistant instructor with Patrick Reynolds, MD in guiding First Year MD students through clinical cases concerning dyspnea.

Wake Forest School of Medicine Orientation, Presenter — 8/2016

- Presented a lecture on Integrative Learning to MD class 2020 during orientation.

Wake Forest School of Medicine Tutoring Services, Tutor

- Tutored first and second year MD students in various topics including a variety of coursework subjects (Biochemistry, Genetics, Gastroenterology, Neurology), time management in medical school, and study planning. 5/2018-Present

HEALTH RELATED LEADERSHIP AND SERVICE

Navigating Medical School (NMS), Wake Forest School of Medicine, *Guides Program Leader and President* 8/2017-Present

- As a Guides Program leader, conducted various leadership duties to pair upperclassmen MD students (guides) with incoming MD students as well as facilitate leadership meetings, lead didactic sessions on mentoring, and ensure the wellbeing of all students involved in the program. As President, acted as point of contact for NMS to Wake Forest School of Medicine administration, scheduled and led NMS leadership meetings, and oversaw NMS progress toward yearly goals.

Pediatric Clerkship Advisory Team, *Student Representative* 6/2018-Present

- The Pediatric Clerkship Advisory Team is made up of 2 each of pediatric faculty, residents, and 4th year medical students. The chief aim of the team is to better the educational experience for 3rd year students on their pediatrics clerkship

Wake Forest School of Medicine MD Program Office of Admissions, *Student Interviewer and Class of 2020 Student Representative on Admission Committee* 9/2018-Present

- Grade students as they go through Multiple Mini Interviews (MMI) during their interview day at Wake Forest School of Medicine. Additionally, in the 2019-2020 admission cycle, was chosen by faculty to be Class 2020 student representative on the Committee of Admissions.

PUBLIC HEALTH EXPERIENCE

WFSM DEAC Clinic, *Student Volunteer*, Winston-Salem, NC 6/2015-Present

- Delivering Equal Access to Care (DEAC) is a free clinic run by Wake Forest School of Medicine students for those in the community of Winston Salem and surrounding areas.
- Triage patients with acute and chronic conditions, obtained histories, and conducted physical examinations.

EMPLOYMENT

ExamKrackers®, *MCAT Instructor,* Winston-Salem, NC 5/2015-8/2015

- Served as instructor of Biological Sciences and Verbal Reasoning content for the Wake Forest School of Medicine Post-Baccalaureate students.

Toccoa Clinic Medical Associates, *Intern,* Toccoa, Georgia 5/2014-8/2014

- Participated in an educational internship through Toccoa Clinic Medical Associates designed to give prospective medical students background into the business side of medicine.

La Farm Bakery, *Baker, Barista, and Floor Salesman,* Cary, NC 1/2015-6/2015

- Worked a variety of positions including baking bread, preparing specialty coffee drinks, managing the company food truck, delivering wholesale orders, and selling products at the shop and at farmers markets.

Hobson Tennis Academy, *Hitting Partner and Assistant Instructor*, Atlanta, Georgia 5/2012-8/2012

- Trained middle and high school junior tennis players ranked in the top 100 in the United States. Particularly worked with students on fitness, serving and volleying technique, and match play strategy.

HONORS/AWARDS

- **Summa Cum Laude**, Mercer University 8/2011-12/2014
- **Phi Kappa Phi Honor Society,** Mercer University 5/2014-Present

- **Medical Student Research Program,** Wake Forest School of Medicine 5/2016-8/2016
  $4,000 research stipend awarded for proposal: *The Effects of Religious Involvement on HIV Management Outcomes Among HIV-positive Adults in Central North Carolina: A Pilot Cross-sectional Study.*