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Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

Geriatric assessment predicts non-fatal toxicities and survival for intensively treated older adults with AML

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Gi-June Min (Seoul St. Mary's Hospital, Korea, Republic of) Byung-Sik Cho (Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea, Republic of) Sung-Soo Park (Seoul St. Mary's Hospital, Korea, Republic of) Silvia Park (Seoul St. Mary's Hematology Hospital, Leukemia Research Institute, College of Medicine, The Catholic,) Young-Woo Jeon (Catholic Blood and Marrow Transplantation Center, Department of Hematology, Seoul St. Mary's Hospita,) Seung-Hwan Shin (Catholic BMT Center, Seoul St. Mary¡¯s Hospital, College of Medicine, The Catholic University of Kor, Korea, Republic of) Seung-Ah Yahng (Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea, Republic of) Jae-Ho Yoon (Catholic Hematology Hospital, Korea, Republic of) Sung-Eun Lee (Catholic Blood and Marrow Transplantation Center, Korea, Republic of) Ki-Seong Eom (Catholic Hematology Hospital, Seoul St. Mary's Hospital, Korea, Republic of) Yoo-Jin Kim (The Catholic University of Korea, Korea, Republic of) Seok Lee (Catholic Hematology Hospital, Korea, Republic of) Chang-Ki Min (Seoul St. Mary's Hospital, Korea, Republic of) Seok-Goo Cho (Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, Korea, Republic of) Dong-Wook Kim (Seoul St. Mary's Hospital, Leukemia Research Institute, The Catholic University of Korea, Korea, Republic of) Jong Wook Lee (Seoul St. Mary's Hospital, The Catholic University of Korea, Korea, Republic of) Hee-Je Kim (Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea, Republic of)

Abstract:
Given a few prospective studies with conflicting results, we investigated the prognostic value of multi-parameter geriatric assessment (GA) domains on tolerance and outcomes after intensive chemotherapy in older adults with acute myeloid leukemia (AML). Newly diagnosed AML aged over 60 years who received intensive chemotherapy consisting of cytarabine and idarubicin (n=105) were enrolled prospectively. Pretreatment GA included evaluations for social and nutritional support, cognition, depression, distress, and physical function. The median age was 64 years (range, 60-75), and 93% had an Eastern Cooperative Oncology Group score <2. Between 32.4% and 69.5% of patients met the criteria for impairment for each domain of GA. Physical impairment by the Short Physical Performance Battery (SPPB) and cognitive dysfunction by the Mini-Mental State Examination in the Korean version of the CERAD Assessment Packet (MMSE-KC) were significantly associated with non-fatal toxicities, including grade III-IV infections (SPPB, P=0.024; MMSE-KC, P=0.044), acute renal failure (SPPB, P=0.013), and/or prolonged hospitalization (³40 days) during induction chemotherapy (MMSE-KC, P=0.005). Reduced physical function by SPPB and depressive symptoms by the Korean version of the short form of geriatric depression scales (SGDS-K) were significantly associated with inferior survival (SPPB, P=0.027; SGDS-K, P=0.048). Gait speed or sit-and-stand speed was the single powerful tool to predict survival outcomes. Notably, the addition of SPPB and SGDS-K, gait speed and SGDS-K, or sit-and-stand speed and SGDS-K significantly improved the power of existing survival prediction models. In conclusion, GA improved risk stratification for treatment decisions and may inform interventions to improve outcomes for older adults with AML. This study was registered at the Clinical Research Information Service (KCT0002172).

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Gi-June Min,[1,2] Byung-Sik Cho,[1,2] Sung-Soo Park,[1,2] Silvia Park,[1,2] Young-Woo Jeon,[3] Seung-Hwan Shin,[4] Seung-Ah Yahng,[5] Jae-Ho Yoon,[1,2] Sung-Eun Lee,[1,2] Ki-Seong Eom,[1,2] Yoo-Jin Kim,[1,2] Seok Lee,[1,2] Chang-Ki Min,[1,2] Seok-Goo Cho,[1] Dong-Wook Kim,[1,2] Jong Wook Lee,[1] and Hee-Je Kim.[1,2]

[1]Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Leukemia Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [3]Department of Hematology, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [4]Department of Hematology, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [5]Department of Hematology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea;

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Corresponding Author

Byung-Sik Cho, M.D., Ph.D., Department of Hematology, Catholic Hematology Hospital, Leukemia Research Institute, College of Medicine, The Catholic University

of Korea, 222, Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea. Telephone: +82-2-2258-6072 / Fax: +82-2-599-3589. E-mail: cbscho@catholic.ac.kr

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Key Points

1. Geriatric assessment focusing on physical function and depression improves the power of survival prediction models for older AML patients.

2. Cognitive and physical impairments are associated with non-fatal toxicities during induction chemotherapy in older AML patients.

Abstract

Given a few prospective studies with conflicting results, we investigated the prognostic value of multi-parameter geriatric assessment (GA) domains on tolerance and outcomes after intensive chemotherapy in older adults with acute myeloid leukemia (AML). Newly diagnosed AML aged over 60 years who received intensive chemotherapy consisting of cytarabine and idarubicin (n=105) were enrolled prospectively. Pretreatment GA included evaluations for social and nutritional support, cognition, depression, distress, and physical function. The median age was 64 years (range, 60-75), and 93% had an Eastern Cooperative Oncology Group score <2. Between 32.4% and 69.5% of patients met the criteria for impairment for each domain of GA. Physical impairment by the Short Physical Performance Battery (SPPB) and cognitive dysfunction by the Mini-Mental State Examination in the Korean version of the CERAD Assessment Packet (MMSE-KC) were significantly associated with non-fatal toxicities, including grade III-IV infections (SPPB, P=0.024; MMSE-KC, P=0.044), acute renal failure (SPPB, P=0.013), and/or prolonged hospitalization (≥40 days) during induction chemotherapy (MMSE-KC, P=0.005). Reduced physical function by SPPB and depressive symptoms by the Korean version of the short form of geriatric depression scales (SGDS-K) were significantly associated with inferior survival (SPPB, P=0.027; SGDS-K, P=0.048). Gait speed or sit-and-stand speed was the single powerful tool to predict survival outcomes. Notably, the addition of SPPB and SGDS-K, gait speed and SGDS-K, or sit-and-stand speed and SGDS-K significantly improved the power of existing survival prediction models. In conclusion, GA improved risk stratification for treatment decisions and may inform interventions to improve

outcomes for older adults with AML. This study was registered at the Clinical Research Information Service (KCT0002172).

Introduction

Acute myeloid leukemia (AML) is a disease of the elderly with a median age of diagnosis between 68 and 72 years.[1,2] Older adults with AML, usually defined as aged 60 years and older, have worse survival outcomes than younger AML patients due to their different biology, with more frequent unfavorable cytogenetics, a decline in performance status, and acquired comorbidities.[3] The mutational spectrum in older adults with AML also differs from that in younger patients,[4] and differentiated mutational patterns could aid precise prognostication.[5] Selected cases of older adults with AML can benefit from intensive chemotherapy, including that containing anthracycline and cytarabine, despite the risk for increased toxicity from treatment.[3,6,7] Several prognostic models have been developed to identify patients at high risk of early death, treatment resistance, or poor survival after conventional intensive AML therapy.[8] However, they were limited by low accuracy and the need for reassessment to reflect changes resulting from continuous improvement in supportive care.[8]

Chronological age, performance status, and comorbidities are employed commonly to determine fitness for intensive treatment. These variables are relatively easy to assess but are limited in capturing the heterogeneity of older patients with hematologic malignancies.[9-11] Therefore, additional assessment tools are needed to better characterize fitness in the context of therapy and to capture the frailty that arises from "decreased reserves in multiple organ systems, which are initiated by disease, lack of activity, inadequate nutritional intake, stress, and/or the physiologic changes by aging."[10,11] Among various frailty assessments, multi-parameter geriatric assessment (GA) offers more comprehensive evaluations, including functional ability,

physical health, cognition, psychological health, nutritional status, and social support.[10,11] Despite the growing evidence of GA to detect unrecognized vulnerabilities in patients with hematologic malignancies to predict treatment tolerance and survival, it is limited by lack of standardization and consensus regarding the prognostic value in older adults with AML.[10,11] Two previous prospective studies for GA in older adults with AML had conflicting results regarding the role of physical performance measures as survival predictors, suggesting the need for further prospective validation for GA.[12,13] Furthermore, it should be determined to what degree preexisting survival prediction models, such as web-based prediction models for AML (AML scores),[14] Ferrara criteria,[15] or Wheatley index,[16] can be improved by integrating components of GA.[8] Here, we reported results of a single-institution prospective cohort study, including newly diagnosed older adults with AML receiving homogeneous intensive induction chemotherapy, to investigate which patient-related characteristics assessed by GA predict treatment tolerance and outcomes and how much they can improve survival prediction tools.

Methods

Study design and population

We performed a single-center prospective cohort study enrolling newly diagnosed older adults with AML aged ≥60 years between November 2016 and December 2019, who underwent intensive induction chemotherapy. Inclusion criteria were as follows: newly diagnosed AML aged between 60 and 75 years, Eastern Cooperative Oncology

Group-Performance Score (ECOG-PS) ≤2, plan for intensive induction chemotherapy, and ability to provide written informed consent and answer various questionnaires. Exclusion criteria were presence of another active malignancy, acute promyelocytic leukemia or AML involving the central nervous system, active infection or uncontrolled bleeding, or impaired organ function such as severe renal, hepatic, or cardiac dysfunction. All patients received induction chemotherapy consisting of idarubicin (12 mg/m^2) for three days plus cytarabine (100 mg/m^2) for seven days.[17] Sixty-one patients (58%) underwent allogeneic stem cell transplantation with suitable donors after 1 or 2 cycles of consolidation.[17] The Institutional Review Board of The Catholic Medical Center approved the current study. All analyses were performed according to the Institutional Review Board guidelines and the tenets of the Declaration of Helsinki. This study was registered at the Clinical Research Information Service (KCT0002172).

GA measures

GA assessments were performed in the inpatient ward by a study nurse at enrollment following published procedures for administration and scoring of each assessment. We performed objective physical performance measurements of handgrip strength and Short Physical Performance Battery (SPPB). Handgrip strength (in kilograms) was measured using a hydraulic grip strength dynamometer performed by a professional rehabilitation medicine doctor.[18] SPPB reliably predicts future disability, hospitalizations, and mortalities among elderly patients, consisting of a gait speed test (4 meter distance), sit-and-stand speed test (repeat 5 times of repeated chair stands maneuver), and balance tests (subdivide to side by side stand, semi-tandem stand, and tandem stand balancing for 10 seconds each) - each measurement was scored

from 0 to 4 (0 is unable to complete the test and 4 is the highest performance level), with a total score ranging from 0 to 12.[19] SPPB, gait speed, and sit-and-stand speed were analyzed as categorical variables using cutoffs of ≤8, ≤3, and ≤3, respectively, for impairment. Cognitive function was assessed using the Mini-Mental State Examination in the Korean version of the CERAD Assessment Packet (MMSE-KC), which has been used widely and validated in the Korean population to measure cognitive impairment.[20] MMSE-KC comprehensively evaluates a different subset of cognitive status, including attention, language, memory, orientation, and visuospatial proficiency. We also utilized the Korean version of the Nursing Delirium-Screening Scale (KNU-DESC), a recently developed accurate but straightforward and sensitive screening instrument for detecting cognitive impairment especially early delirium. KNU-DSEC consists of 5 categories of assessment: disorientation, inappropriate behavior or communication, illusions/hallucinations, and psychomotor retardation.[21] For psychological function, we used two scales of the Korean version of the Short-form Geriatric Depression Scale (SGDS-K), focused on depressive symptoms of old-aged populations, and Patient Health Questionnaire-9 (PHQ-9), more generalized screening tools of depression and related psychologic diagnoses.[22,23] In addition, we utilized the National Comprehensive Cancer Network's Distress Thermometer (NCCN-DT) screening measure to identify and address psychological distress.[24] Social and nutritional support was evaluated with the Older Americans Resources and Services (OARS) and the Mini Nutritional Assessment (MNA), respectively.[25,26] Nutritional support and bedside or ambulatory physical tranining program by expert therapists were provided based on referral. Psychiatrists were involved in treatment only when

referred for psychological symptoms. MMSE-KC, KNU-DESC, SGDS-K, PHQ-9, NCCN-DT, OARS, and MNA were analyzed as categorical variables using cutoffs of ≤23, ≥2, ≥6, ≥6, ≥3, ≥18, and ≤23.5, respectively, for impairment.

Covariates

Patient-specific variables (echocardiogram, pulmonary function test, and body temperature) and AML-specific variables (white blood cell count, platelet count, lactate dehydrogenase level, prior myelodysplastic syndrome or other malignancy histories, cytogenetic abnormalities, and genetic mutations screened by real time-quantitative polymerase chain reaction or next-generation sequencing [NGS] panel customized for acute leukemia[27]) were collected from medical records. The attending physician's estimate of ECOG-PS at admission was recorded and categorized as good functional status (score ≤1) or poor functional status (score >1). Comorbidity burden was scored using the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI).[28] Those variables were utilized to categorize patients through preexisting survival prediction models: AML scores,[14] Ferrara criteria,[15] Wheatley index,[16] and ELN 2017 risk classification.[29]

Outcomes and definitions

The primary outcomes were overall survival (OS) defined as the date of diagnosis to the date of death or last follow-up for censored patients. The secondary outcomes were early death (ED),[12] defined as death within 60 days after induction chemotherapy, complete remission (CR), and non-relapse mortality (NRM). We defined CR as a morphologic leukemia-free state with <5% blasts in the bone marrow and no persistent

extramedullary disease. NRM was empirically defined as death for any reason without evidence of disease recurrence, and is calculated by cumulative incidence estimation, treating relapse as a competing risk. The adverse events were evaluated by the National Cancer Institute's Common Terminology Criteria (version 4.0), where non-fatal toxicity was graded from I to IV, while fatal toxicity was grade V.

Statistical analysis

The categorical variables were compared using a Chi-square analysis and Fisher's exact test, and continuous variables were assessed using Student's t-test and the Wilcoxon rank-sum test. OS was estimated using Kaplan-Meier analysis, and the difference in survival between the groups was compared using a log-rank analysis. NRM was assessed using a cumulative incidence estimation method, and comparisons of NRM between the groups were based on Gray's competing risk method. The multivariate logistic regression was used to examine baseline GA measurements as predictors of adverse events during induction chemotherapy including infection, acute renal failure, hepatotoxicity, gastrointestinal complications, and prolonged hospitalization longer than 40 days. We also examined survival (OS and NRM) predictors by comparing available clinical variables such as baseline characteristics, GA measurements, and preexisting survival prediction models. Variables found to be significant in the univariate model were included in a multivariable model. Highly correlated variables were evaluated by the correlation coefficient of each predictor. We designed separate multivariate models for highly correlated variables. Multivariate models were derived using stepwise selection among candidate variables with the Wald test for overall p-value for factors with >2

levels and p-value <0.05 to warrant inclusion in the model. To assess the incremental impact of score variables on predicting survival, we used Integrated Discrimination Improvement (IDI) as described for survival analysis by Chambless et al.[30] Statistical significance was determined as a P value <0.05 (two-tailed). All statistics were conducted using SPSS, version 13.0 (SPSS, Inc., Chicago, IL) and R-software (version 3.4.1, R Foundation for Statistical Computing, 2017).

Results

Demographics

The screening and enrollment of the potentially eligible participants are illustrated in Supplementary Figure A. A total of 202 patients was diagnosed during the study period, 125 patients were eligible, and 105 patients agreed to participate. Ineligible patients received non-intensive chemotherapy (n=60; decitabine, n=53; low dose cytarabine, n=3; azacitidine, n=3, and gilteritinib, n=1) or best supportive care (n=17; poor ECOG-PS, n=12; refusal of any chemotherapy, n=5). The baseline characteristics are described in Table 1. Among the 105 enrolled patients, the median age was 64 years (range, 60–75) and 61.9% were male. Based on the ELN 2017 risk classification, 30.5% of the patients exhibited poor risk features, and 30.5% were secondary AML. We classified patients by the existing survival prediction models (Table 1). The Wheatley index is a model used for survival of older adults with AML by large cohorts of the Medical Research Council AML11 and the Leukemia Research Fund AML 14 trials.[16] By the Wheatley index, 21.9% were at poor risk. AML scores through a web-based

application for risk assessment of intensive chemotherapy in older adults with AML were available to predict not only the probability of CR and the risk of ED, but also survival.[14] Median AML scores for CR and ED were 61.3% (range, 14.5-90.6) and 18.9% (range, 6.1-52.4), respectively. Ferrara criteria,[15] which include 9 covariates to classify fitness for intensive chemotherapy based on risks for ED and OS, classified 26.7% of patients as unfit.

GA measures

All enrolled patients participated in GA and answered various questionnaires without missing data. The median time from admission to administration of GA was three days (range, 2 to 7), and approximately 40 minutes (a minimum of 30 minutes to a maximum of 1 hour) were spent evaluating each patient on GA. Induction chemotherapy commenced one day after completion of GA measurement. The baseline GA scores are presented in Table 2. Almost all patients (92.4%; Supplementary Figure B) had various impairments in physical function (57.6%), nutritional status (33.3%), social support (32.4%), cognitive function (34.0%), and psychological function (depressive symptoms or distress; 69.5%). Regarding physical function, 35.2% exhibited impairment by objectively measured SPPB, whereas 9.5% of K-MBI and 29.5% of K-IADL self-reported measures captured recalled function status. Correlation analysis (Supplementary Table A) revealed that impairments in SPPB were correlated with all other measures of physical function. Domains of physical function were correlated commonly with impairments in cognition (MMSE-KC), depression (SGDS-K and PHQ-9), and nutrition (MNA).

Treatment tolerance during induction chemotherapy according to GA measures

Clinical outcomes and adverse events during induction chemotherapy are listed in Supplementary Table B. The median recovery period for neutrophil and platelet counts was 26 (range, 24-29) and 30 (range, 29-34) days, respectively, during induction chemotherapy. The median hospitalization for induction chemotherapy was 32 days (range, 16-104 days). In our cohort, 65.7% achieved CR1, 4.8% experienced ED within 60 days, and 58.1% underwent transplantation. Clinical outcomes and adverse events according to baseline characteristics and GA measures are listed in Supplementary Table C. Among the baseline characteristics, poor ECOG-PS and high HCT-CI scores were associated with grade III-IV acute renal failure (21.1% vs. 3.5%, P=0.019) and gastrointestinal complications (29.7% vs. 12.2%, P=0.037), respectively. Among the GA measures, impairments in physical function as measured by SPPB (72.9% vs. 58.8%, P=0.021) and K-IADL (80.6% vs. 60.8%, P=0.049), and cognitive impairment by MMSE-KC (80.0% vs. 60.0%, P=0.040) were associated with grade III-IV infection. Physical dysfunction measured by SPPB also was associated with grade III-IV acute renal failure (32.4% vs. 10.3%, P=0.005). Prolonged hospitalization from various adverse events was defined that longer than 40 days (75th percentile) and was associated with poor ECOG-PS (17.4% vs. 3.7%, P=0.040) and impairment in MMSE-KC (40.0% vs. 12.9%, P=0.002). On multivariate analysis adjusted for age, ECOG-PS, and HCT-CI (Figure 1), impairments in MMSE-KC (odds ratio [OR] 2.7, 95% confidence interval [CI], 1.0–6.9, P=0.044) and SPPB (OR 3.0, 95% CI 1.2–7.8, P=0.024) were associated with grade III-IV infection, and SPPB was associated with grade III-IV acute renal failure (OR 3.9, 95% CI 1.3–11.4, P=0.013). The MMSE-KC was significantly associated with prolonged hospitalization (OR 4.2, 95% CI 1.5–4.2,

P=0.005). Indeed, among 35 patients who had cognitive impairment on MMSE-KC, 13 developed delirium during induction chemotherapy, which was more frequent than in non-impaired patients (37.1% vs. 12.9%, P=0.004).

Survival outcomes according to GA measures

With a median follow-up of 13.7 months (range, 0.2-48.3), the cohort median OS was 24.9 months. However, median NRM was not reached in this study. The 2-year estimated OS and NRM were 52.2% (95% CI 41.5 – 61.8) and 36.5% (95% CI 26.9 – 46.2), respectively. Among the GA measures, physical (SPPB; gait speed and sit-and-stand speed test as a part of SPPB), psychological function (SGDS-K), and nutrition (MNA) were significantly associated with OS and/or NRM on univariate analysis (Supplementary Table D and Figure 2). Due to the significant correlations between those measures (Supplementary Table A), we performed multivariate analysis of each GA measure with other significant covariates (Figure 3). In multivariate analysis model #1, patients with impaired physical function by SPPB had 1.9-fold and 2.0-fold higher risk of death (95% CI 1.1–3.4, P=0.027) and NRM (95% CI 1.1–3.9, P=0.033), respectively. Patients with impaired gait (model #2) and sit-and-stand (model #3) speed had 2.-fold (95% CI 1.5–5.2, P=0.002) and 3.6-fold (95% CI 1.9–7.0, P<0.001) higher risk of death and 2.5-fold (95% CI 1.2–4.9, P=0.011) and 3.8-fold (95% CI 1.8–8.2, P<0.001) higher risk of NRM, respectively. Patients with depressive symptoms based on the SGDS-K (model #4) exhibited a 1.9-fold higher risk of death (95% CI 1.0–3.6, P=0.048) and a trend of higher NRM (hazard ratio 1.8, 95% CI 0.9–3.5, P=0.097). Overall, 48 patients were referred to psychiatrists due to psychological symptoms during treatment, and 15 patients were confirmed with major depressive

disorder (MDD) during the post-remission treatment course. All patients with MDD died, mostly due to NRM (71.1%). Among 19 patients impaired by SGDS-K, six developed MDD, which was more frequent than in non-impaired patients (31.6% vs. 10.5%, P=0.028). Nutrition impairment by MNA (model #5) was significantly associated with a 2.1-fold higher risk of NRM (95% CI 1.1–4.0, P=0.024).

Improvement of existing survival prediction models by GA measures

We evaluated the prognostic values of the existing survival prediction models (Supplementary Table E). The Wheatley index and AML scores were significantly associated with worse OS. Figure 4 (and Supplementary Table F) presented the explanatory power of survival prediction models and GA measures for OS. The IDI can be interpreted as the proportion of variance explained by the model, similar to r^2, which is a measure of how well a regression line fits the data points in linear regression. The Wheatley index score explained 32.1% of the variability in OS. The addition of SPPB/SGDS-K explained an additional 10.1%. The addition of gait speed/SGDS-K or sit-and-stand speed/SGDS-K explained an additional 14.8% or 19.1% explanatory power of the Wheatley index score. Another prediction model of AML scores for ED exhibited similar results. The addition of SPPB/SGDS-K, gait speed/SGDS-K, or sit-and-stand speed/SGDS-K explained an additional 10.0%, 17.5%, and 23.2% of variability, respectively. On the other hand, AML scores for CR demonstrated an additional 10.5% or 13.7% explanatory power on addition of gait speed/SGDS-K or sit-and-stand speed/SGDS-K. However, adding SPPB/SGDS-K did not significantly improve the explanatory power.

Discussion

The role of physical performance measures as survival predictors has been controversial in intensively treated older adults with AML. Klepin et al. reported the first prospective data to investigate the predictive value of GA measures in older adults with AML (median age of 69 years; 10.8% of eighties; 78.1% of ECOG-PS ≤1) showing physical function as predictors for survival.[12] However, another prospective study by Timilshina et al. select older adults with AML (median age of 68 years; no eighties; 85.6% of ECOG-PS ≤1) showed that physical performance measures were not good predictors of OS.[13] Those studies were different in patient selection and limited by the relatively small cohort and lack of information about mutational status, requiring further validation. Given that previous studies for GA measures in older adults with AML pertain to Western countries, GA must be validated in non-Western countries based on varied outcomes by region due to differences in the referral system,[31] genetic background,[32,33] and socioeconomic status.[34,35] Our Korean cohort was characterized by relatively younger age (median age of 64 years and no eighties), good performance status (ECOG-PS ≤1, 93.3%), and data about mutational status compared to the aforementioned prospective studies.[12,13] Among the GA measures, objectively measured physical dysfunction by SPPB was significantly associated with worse NRM and OS, suggesting that physical function is a good predictor for survival even in relatively younger patients with better ECOG-PS scores. Of note, gait speed among the SPPB battery was the single measure associated with worse NRM and OS in our cohort, which is in line with a recent prospective study in patients with hematological malignancies aged 75 years and older treated at varying intensities.[36] In addition, sit-

and-stand speed, another component of SPPB, had a similar prognostic impact in NRM and OS to gait speed. These results clarified the role of physical function as survival predictors in intensively treated older adults with AML and highlighted the potential of gait or sit-and-stand speed as a simple measure for frailty.

Our study also highlights the prognostic significance of depressive symptoms for survival. There were reports of the association between depression and mortality in various cancer types, but few in AML.[37,38] Klepin et al. reported that depressive symptom burdens at remission were associated not only with functional decline after induction chemotherapy[39] but also mortality.[40] However, they did not find an association between depression prior to treatment and mortality partly due to the small cohort.[12,39,40] In our cohort, baseline depressive symptoms measured by SGDS-K were associated with worse survival. SGDS-K is a screening tool specialized for depression of the older population. To the best of our knowledge, this is the first prospective study demonstrating the prognostic value of baseline emotional health in older adults with AML. Our data showed that patients with increased depressive symptom burdens by SGDS-K were more frequently diagnosed with MDD during the post-remission treatment course. Indeed, all patients diagnosed with MDD during the treatment course died, mostly due to NRM. Depression could influence cancer mortality through a pathophysiological effect via neuroendocrine and immunological functions or from weakening adherence to preventive screening procedures, AML treatments, or recommendations for maintaining health.[37] Depressive symptoms can be a proxy for disease severity due to similarity to the side effects of treatment or cancer symptoms. Therefore, screening for depression should be conducted routinely,

and referrals to mental health specialists should be considered. Prognostic significance of dynamic changes in depressive symptoms should be evaluated further by repeat GA at each step of the treatment course in larger cohorts. Moreover, our data suggest the necessity of further studies to determine if interventions targeting emotional as well as functional health can improve survival outcomes.

It is notable that cognitive impairment was not associated with worse survival in our cohort, in contrast to data from Klepin et al.[12] The proportion of patients with cognitive dysfunction was similar between the two studies despite the difference in age distribution. Cognitive test score can identify a patient who either has, or is at risk for, delirium, which is a known risk factor for mortality among hospitalized older patients with other medical conditions.[41] Our data showed the relationship between baseline cognitive performance and subsequent development of delirium during the treatment course. However, delirium was not associated with survival outcomes in our cohort. Given the inclusion of older population with worse ECOG-PS scores in the cohort of Klepin et al., the influence of baseline cognitive impairment on survival might be more significant in older populations of AML, suggesting heterogeneity among the older AML population, which should be confirmed through a large scale study. On the other hand, our data suggest that cognitive impairment was associated with treatment tolerance or resilience. We observed that patients with cognitive impairment were exposed to increased risk for grade III-IV infectious complications and had prolonged hospitalization during induction chemotherapy, which might be related with increased incidence of delirium during induction chemotherapy. In addition, impaired physical function measured by SPPB was associated with grade III-IV acute renal failure and

infection. The association between these non-fatal toxicities and patient characteristics has received little attention.[8] Our data suggest that cognitive and functional measures by GA are available to identify patients at risk of severe toxicities following intensive chemotherapy in older adults with AML, with those patients possibly being preferred candidates for low-intensity combined therapies.[42] Further large studies are warranted to confirm the feasibility of GA measures as predictors of non-fatal toxicities.

Among existing survival prediction models,[14-16,43] AML scores[14] and the Wheatley index[16] were useful in our cohort. Of note, our data showed that addition of SPPB/SGDS-K, gait speed/SGDS-K, or sit-and-stand speed/SGDS-K significantly improved the predictive power of those survival prediction models, with 10 to 23% of absolute additional variability. These results are strong evidence for the need to incorporate GA into validated survival prediction models to determine initial treatment, such as intensive induction chemotherapy or low-intensity therapies, in practice and clinical trials for older adults with AML. For example, older adults with AML may be offered combination therapy with venetoclax and hypomethylating agents with its proven safety profile and outcome,[42] rather than intensive chemotherapy if the GA combined model-based risk of death were high.

The strengths of our study include its prospective nature, a high participation rate, and the scarcity of GA research conducted in Asian cohorts. In particular, our cohort included AML aged between 60 and 75 years who were the main subjects of intensive induction chemotherapy. Such a cohort is more practical and applicable than previous prospective studies that included AML aged over 75 years, even into the

eighties.[10,11] In addition, we reassessed the existing prognostic models with a cohort of mutational profiles representing recent advances in supportive care and objectively demonstrated how much the GA measures improved predictability. Nonetheless, the modest size of the cohort and data from a single institution could limit its generalizability, warranting larger prospective studies from multiple institutions.

In summary, we prospectively demonstrated the prognostic value of physical and psychological assessments by GA for survival outcomes in intensively treated older adults with AML. Particularly, gait speed or sit-and-stand speed was the single powerful tool to identify frailty and predict survival. Cognitive and physical impairments were available to identify non-fatal toxicities during intensive chemotherapy. Our data will facilitate the incorporation of GA measures into validated survival prediction models to determine the initial treatment for older adults with AML in routine clinical care and clinical trials. Further studies are warranted to determine the best ways to adjust the care provided for frail patients to improve treatment tolerance and outcomes.

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Authorship

Conception and design: B.S. Cho

Development of methodology: B.S. Cho, G.J. Min

Acquisition of data: B.S. Cho, G.J. Min, K.S. Eom, Y.J. Kim, S. Lee, C.K. Min, S.G. Cho, D.W. Kim, J.W. Lee, H.J. Kim

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B.S. Cho, G.J. Min, H.J. Kim

Writing, review, and/or revision of the manuscript: B.S. Cho and G.J. Min

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.H. Shin, S.A. Yahng, S. Park, S.S. Park, Y.W. Jeon, J.H. Yoon, S.E. Lee

Study supervision: B.S. Cho

Conflict of interest

The authors declare that they have no personal or financial conflict of interest.

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Table 1. Baseline characteristics of the study cohort (N=105)

Characteristics	
Age at diagnosis (range), years	64 (60 – 75)
60-64 years	54 (51.4%)
65-70 years	37 (35.3%)
71-75 years	14 (13.3%)
Gender	
Male / Female	65 (61.9%) / 40 (38.1%)
Disease type	
de novo AML	73 (69.5%)
Secondary AML	32 (30.5%)
ELN 2017 criteria	
Favorable	24 (22.9%)
Intermediate	49 (46.7%)
Poor	32 (30.5%)
Genetic mutation	
Biallelic *CEBPA*	6 (5.7%)
NPM1 without *FLT3-ITD* or with *FLT3-ITD* (low)	13 (12.4%)
NPM1 with *FLT3-ITD* (high)	10 (9.5%)
FLT3-ITD (high) without *NPM1*	9 (8.6%)
RUNX1	10 (9.5%)
ASXL1	9 (8.6%)
TP53	2 (1.9%)
Laboratory finding at baseline	
WBC, x 10^9/L (range)	3.8 (0.3 – 345.7)
Hemoglobin	9.1 (5.2 – 13.0)
Platelet count, x 10^9/L (range)	68.0 (9.0 – 827.0)
Creatinine (mg/dL)	0.9 (0.5 – 1.7)
Albumin (g/dL)	3.8 (2.8 – 5.0)
Fibrinogen, mg/dL	344.0 (57.0 – 500.0)
Lactate dehydrogenase, U/L	471.0 (184.0 – 13200.0)
Basic assessment	
Cardiac function, LVEF (%)	64.0% (52.0 – 74.2)
Pulmonary function	
FEV1 (%)	88.0% (57.0 – 115.0)
DLCO/Adj. (%)	77.0% (42.0 – 119.0)
ECOG performance status	
0-1 / 2	98 (93.3%) / 7 (6.7%)
HCT-CI	
HCI-CI ≥3 / ≥4 / ≥5	24 (22.9%) / 15 (14.3%) / 9 (8.6%)
Wheatley index§	
Score, median (range)	7 (4 – 14)
Good risk (4-6)	52 (49.5%)
Standard risk (7-8)	30 (28.6%)
Poor risk (≥9)	23 (21.9%)
AML scores*	

ED Score, median, % (range)	18.9% (6.1 – 52.4)
1st IQR / 2nd IQR / 3rd IQR / 4th IQR	26 (24.8%) / 26 (24.8%) / 24 (22.9%) / 29 (27.6%)
CR Score, median, % (range)	61.3% (14.5 – 90.6)
1st IQR / 2nd IQR / 3rd IQR / 4th IQR	27 (25.7%) / 26 (24.8%) / 28 (26.7%) / 24 (22.8%)
Ferrara criteria†	
Components	
Age ≥75 years	1
Performance status (ECOG) ≥3	0
Heart (LVEF ≤50%)	0
Lungs (DLCO ≤65% or FEV1 ≤65%)	21
Kidney (On temporal dialysis)	3
Liver (LFT >3 times normal values)	4
Infection (resistant to anti-infective therapy)	0
Mental illness or uncontrolled cognitive status	0
Any other comorbidity that the physician judges to be incompatible with chemotherapy	0
† Unfit	28 (26.7%)

AML, acute myeloid leukemia; DLCO, diffusing capacity; ECOG, Eastern Cooperative Oncology Group; ED, early death within 60 days after induction; ELN, European leukemia network; FEV1, forced expiratory volume in one second; HCT-CI, hematopoietic cell transplantation-specific comorbidities; IC, intensive chemotherapy; IQR, interquartile range; LVEF, left ventricular ejection fraction

§ Wheatley risk score comprises cytogenetic risk group, WBC group, ECOG performance status, age group, and AML type (Ref.) Keith Wheatley, et al., *British Journal of Haematology* 2009; 145, 598-605.

***** AML scores calculate the probability of CR or ED (%) with appropriate formula, including initial body temperature, hemoglobin, platelet count, fibrinogen level, LDH level, age, cytogenetic/molecular risk classification, and AML type. Utz Krug et al., *Lancet* 2010;376:2000-2008.

† Ferrara operation criteria to define unfitness to intensive chemotherapy in AML. The definition of unfitness to intensive chemotherapy should require the fulfillment of at least one of nine criteria. *Leukemia* (2013) 27, 997-999; doi:10.1038/leu.2012.303

Table 2. Baseline geriatric assessment (GA) measures of the study cohort (N=105)

GA score	N (%)
Physical function assessment	
K-MBI as ADL measurement, median (range)	105 (24 - 105)
Impaired K-MBI (≤100)	10 (9.5%)
K-IADL, median (range)	10 (10 – 28)
Impaired K-IADL (≥12)	31 (29.5%)
SPPB, median (range)	10 (3 – 12)
Impaired SPPB (≤8)	37 (35.2%)
Standing balance, consist of 3 subsequent balance test, (≤3 points)	
Side by side stand < 10 sec. (point 0)	0
Semi-tandem stand < 10 sec. (point 0)	3 (2.9%)
Tandem stand < 10 sec.	18 (17.2%)
3.0~9.9 sec. (point 1)	9 (50.0%)
>3.0 sec. or cannot perform (point 0)	9 (50.0%)
Gait speed assessment (4 meters), (≥4.82 sec.)	
<4.82 sec. (point 4)	48 (45.7%)
4.82-6.20 sec. (point 3)	27 (25.7%)
6.21-8.70 sec. (point 2)	14 (13.3%)
>8.70 sec. (point 1)	6 (5.7%)
cannot perform (point 0)	10 (9.5%)
Sit-and-Stand speed, five times, (≥11.19 sec.)	
<11.19 sec. (point 4)	46 (43.8%)
11.19-13.69 sec. (point 3)	21 (20.0%)
13.70-16.69 sec. (point 2)	17 (16.2%)
>16.7 sec. (point 1)	9 (8.6%)
>60 sec. or cannot perform (point 0)	12 (11.4%)
Handgrip strength	
Dominant hand strength, kg, median (range)	28 (12 – 46)
Male, dominant hand strength, kg, median (range)	34 (12 – 46)
Female, dominant hand strength, kg, median (range)	21 (13 – 28)
Impaired handgrip strength, dominant hand (≤ 4th IQR)	24 (22.9%) ; Male 10 / Female 14
Nutritional status assessment	
MNA, median (range)	25.5 (10.5 – 33.0)
Impaired MNA (≤23.5)	35 (33.3%)
Social support assessment	
OARS, median (range)	16 (8 – 24)
Impaired OARS (≥18)	34 (32.4%)
Cognition function assessment	
MMSE-KC, median (range)	26 (15 – 30)
Impaired MMSE-KC (≤23)	35 (33.3%)
No cognitive impairment (24-30)	70 (66.7%)

Mild cognitive impairment (18-23)	31 (29.5%)
Severe cognitive impairment (0-17)	4 (3.8%)
KNU-DESC, median (range)	0 (0 – 3)
Impaired KNU-DESC (≥2)	2 (1.9%)
Psychological function assessment	
SGDS-K, median (range)	2 (0 – 15)
Impaired SGDS-K (≥6, moderate depressive symptom)	19 (18.1%)
No depression (0-5)	86 (81.9%)
Moderate depressive symptom (6-9)	9 (8.6%)
Major depression (≥10)	10 (9.5%)
PHQ-9, median (range)	5 (0 – 27)
Impaired PHQ-9 (≥6, mild depression)	50 (47.6%)
No depression (0-5)	55 (52.4%)
Mild depression (6-8)	18 (17.1%)
Moderate depression (9-14)	19 (18.1%)
Severe depression (≥15)	13 (12.4%)
NCCN distress thermometer, median (range)	3 (0 – 10)
Impaired NCCN distress thermometer (≥3)	64 (61.0%)

ADL, activity of daily living; K-IADL, Korean Instrumental Activities of Daily Living; K-MBI, Korean Version of Modified Barthel Index; KNU-DESC, Korean Nursing Delirium Screening Scale; MMSE-KC, Mini-Mental Status Examination-the Korean version of CERAD Assessment Packet; MNA, Mini Nutritional Assessment; NCCN, National Comprehensive Cancer Network; OARS, older Americans Resources, and Services; PHQ-9, Patient Health Questionnaire-9; SGDS-K, the Korean version of the Short form Geriatric Depression Scale; SPPB, Short Physical Performance Battery

Figure legends

Figure 1. Forest plot of odds ratio for variables associated with treatment tolerance during induction chemotherapy.

Significant variables on univariates analysis were adjusted by age, ECOG-PS, and HCT-CI. Impairments in MMSE-KC and SPPB were associated with grade III-IV infection, and SPPB was associated with grade III-IV acute renal failure. The MMSE-KC was significantly associated with prolonged hospitalization. ECOG-PS, Eastern Cooperative Oncology Group Performance Status; K-IADL, Korean Instrumental Activities of Daily Living; MMSE-KC, Mini-Mental Status Examination-the Korean version of CERAD Assessment Packet; MNA, Mini Nutritional Assessment; SPPB, Short Physical Performance Battery (* $p<0.05$; ** <0.01; *** <0.001).

Figure 2. Kaplan–Meier survival curves according to GA measures.

Kaplan–Meier survival curves according to GA measures for physical function with (A) SPPB, (B) gait speed and (C) sit-and-stand speed as part of SPPB and for depression with (D) SGDS-K scores. Impairments in physical and psychological health were associated with inferior overall survival. GA, geriatric assessment; SGDS-K, the Korean version of the Short form Geriatric Depressive Scale; SPPB, Short Physical Performance Battery.

Figure 3. Forest plot of hazard ratio for variables associated with survival outcomes.

We performed multivariate analysis for survival outcomes with significant variables on univariate analysis. Among GA measures, (A) SPPB, gait speed, sit-and-stand speed,

and SGDS-K impairment were significantly associated with inferior overall survival. (B) SPPB, gait speed, sit-and-stand speed, and MNA impairment were significantly associated with higher non-relapse mortality. AML, acute myeloid leukemia; ECOG-PS, Eastern Cooperative Oncology Group Performance status; MNA, Mini Nutritional Assessment; SGDS-K, the Korean version of the Short form Geriatric Depressive Scale; SPPB, Short Physical Performance Battery (* p<0.05; ** <0.01; *** <0.001).

Figure 4. Explanatory power of known prognostic scoring systems to predict overall survival.

The addition of (A) SPPB and SGDS-K improved the power of existing survival prediction models of Wheatley index (32.1% to 42.2%, p<0.001, AML score for early death (25.7% to 35.7%, p=0.007), but not in AML score for complete remission (37.0% to 41.5%, p=0.093). (B) Adding gait speed and SGDS-K improved the prediction power of Wheatley index (32.1% to 46.9%, p<0.001), AML score for early death (25.7% to 43.2%, p<0.001), and AML score for complete remission (37.0% to 47.5%, p=0.013). (C) Adding sit-and-stand speed and SGDS-K improved the prediction power of Wheatley index (32.1% to 51.2%, p<0.001), AML score for early death (25.7% to 48.9%, p<0.001), and AML score for complete remission (37.0% to 50.7%, p=0.027). (* p<0.05; ** <0.01; *** <0.001).

Figure 1

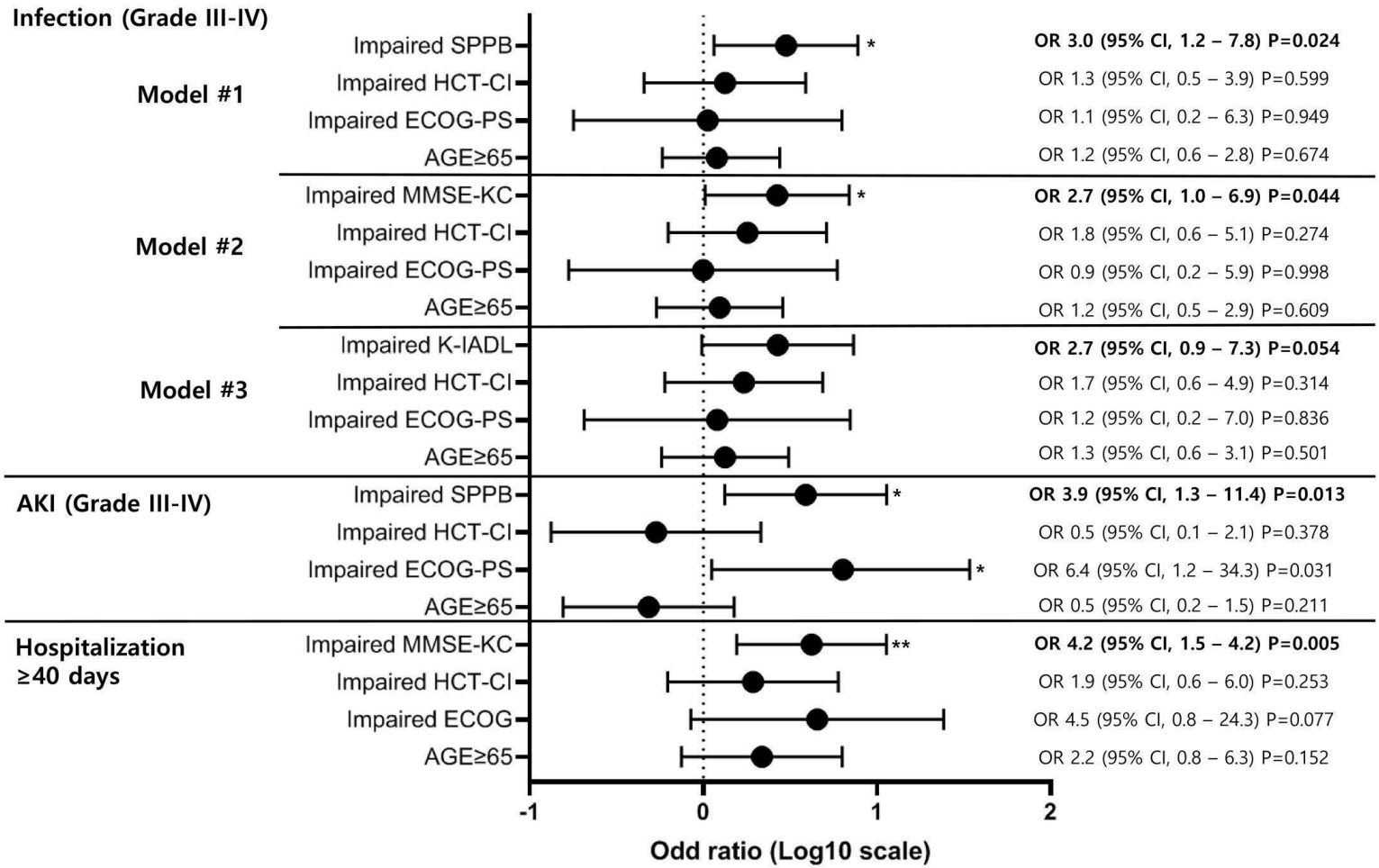

Infection (Grade III-IV)
Model #1
Impaired SPPB
Impaired HCT-CI
Impaired ECOG-PS
AGE≥65
OR 3.0 (95% CI, 1.2 – 7.8) P=0.024
OR 1.3 (95% CI, 0.5 – 3.9) P=0.599
OR 1.1 (95% CI, 0.2 – 6.3) P=0.949
OR 1.2 (95% CI, 0.6 – 2.8) P=0.674
Model #2
Impaired MMSE-KC
Impaired HCT-CI
Impaired ECOG-PS
AGE≥65
OR 2.7 (95% CI, 1.0 – 6.9) P=0.044
OR 1.8 (95% CI, 0.6 – 5.1) P=0.274
OR 0.9 (95% CI, 0.2 – 5.9) P=0.998
OR 1.2 (95% CI, 0.5 – 2.9) P=0.609
Model #3
Impaired K-IADL
Impaired HCT-CI
Impaired ECOG-PS
AGE≥65
OR 2.7 (95% CI, 0.9 – 7.3) P=0.054
OR 1.7 (95% CI, 0.6 – 4.9) P=0.314
OR 1.2 (95% CI, 0.2 – 7.0) P=0.836
OR 1.3 (95% CI, 0.6 – 3.1) P=0.501
AKI (Grade III-IV)
Impaired SPPB
Impaired HCT-CI
Impaired ECOG-PS
AGE≥65
OR 3.9 (95% CI, 1.3 – 11.4) P=0.013
OR 0.5 (95% CI, 0.1 – 2.1) P=0.378
OR 6.4 (95% CI, 1.2 – 34.3) P=0.031
OR 0.5 (95% CI, 0.2 – 1.5) P=0.211
Hospitalization ≥40 days
Impaired MMSE-KC
Impaired HCT-CI
Impaired ECOG
AGE≥65
OR 4.2 (95% CI, 1.5 – 4.2) P=0.005
OR 1.9 (95% CI, 0.6 – 6.0) P=0.253
OR 4.5 (95% CI, 0.8 – 24.3) P=0.077
OR 2.2 (95% CI, 0.8 – 6.3) P=0.152
-1
0
1
2
Odd ratio (Log10 scale)

Figure 2

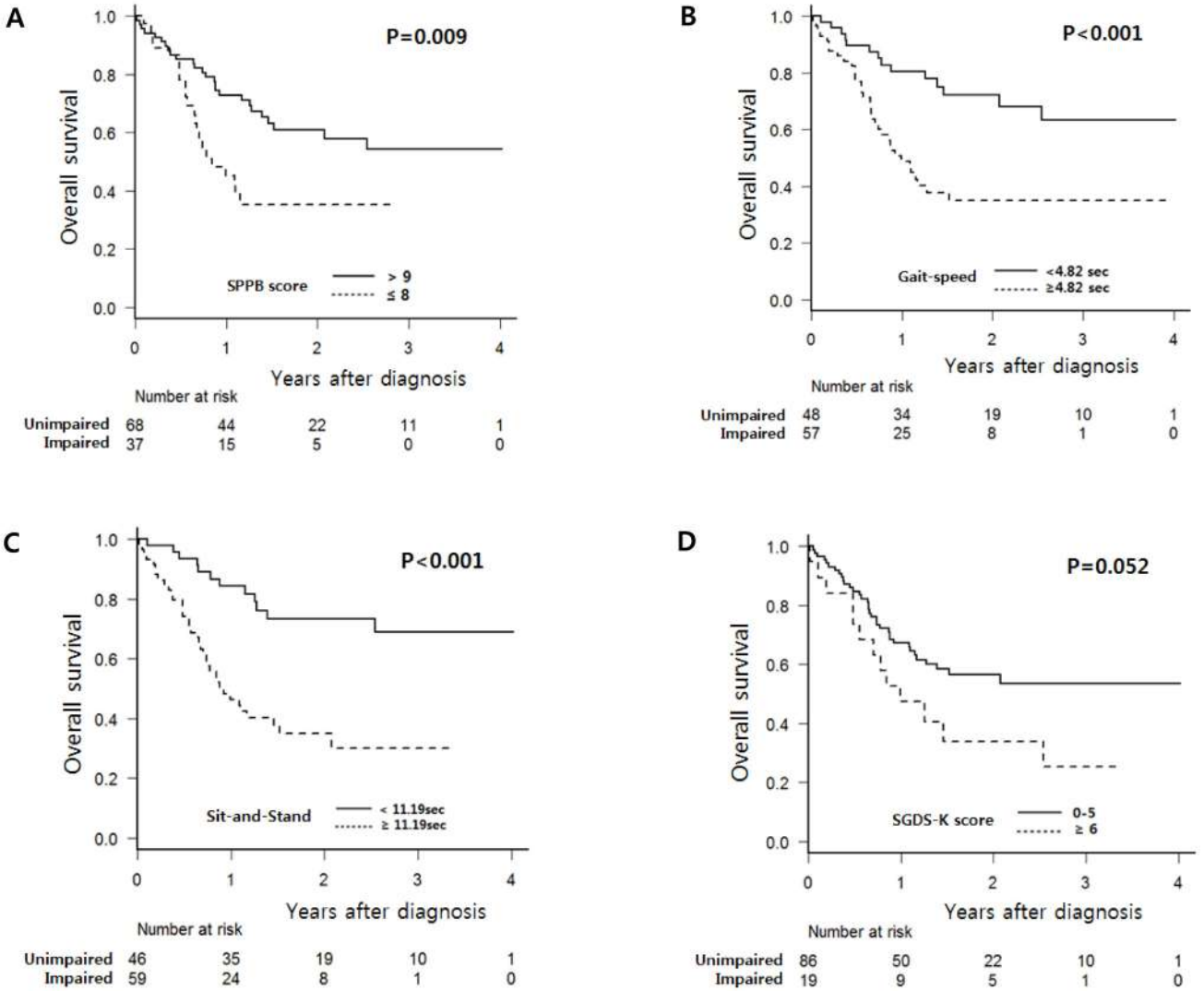
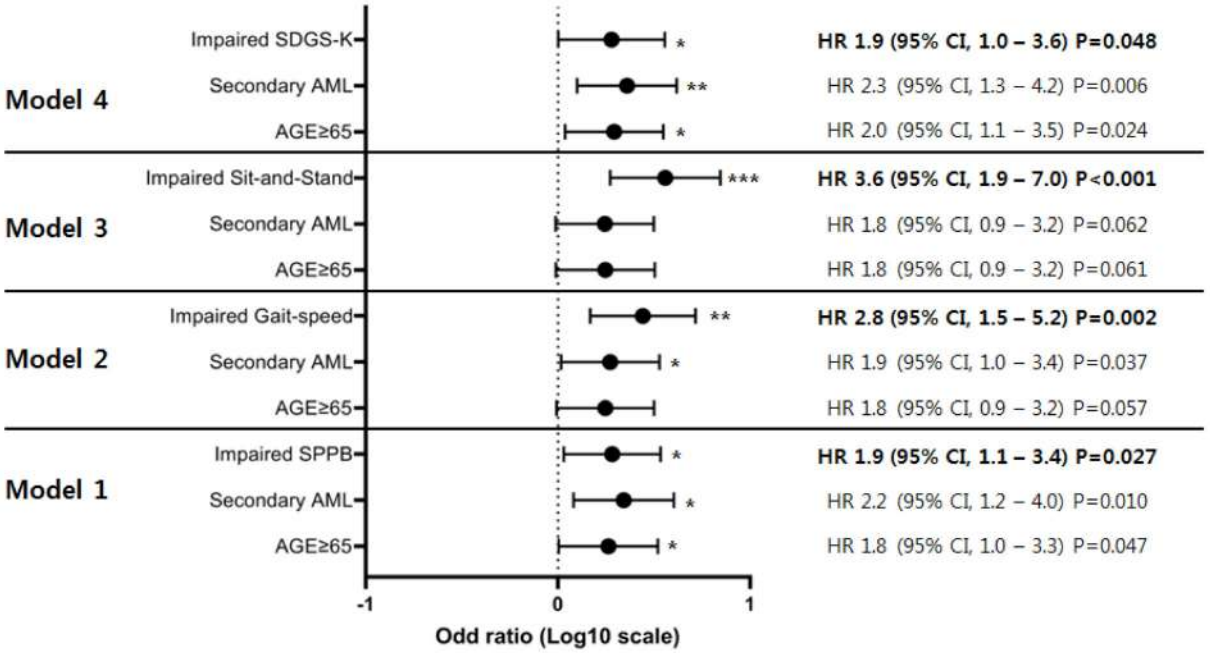

A
P=0.009
Overall survival
SPPB score
> 9
≤ 8
Years after diagnosis
Number at risk
Unimpaired 68 44 22 11 1
Impaired 37 15 5 0 0
B
P<0.001
Overall survival
Gait-speed
<4.82 sec
≥4.82 sec
Years after diagnosis
Number at risk
Unimpaired 48 34 19 10 1
Impaired 57 25 8 1 0
C
P<0.001
Overall survival
Sit-and-Stand
< 11.19sec
≥ 11.19sec
Years after diagnosis
Number at risk
Unimpaired 46 35 19 10 1
Impaired 59 24 8 1 0
D
P=0.052
Overall survival
SGDS-K score
0-5
≥ 6
Years after diagnosis
Number at risk
Unimpaired 86 50 22 10 1
Impaired 19 9 5 1 0

Figure 3

A

Overall survival



B

Non-relapse mortality

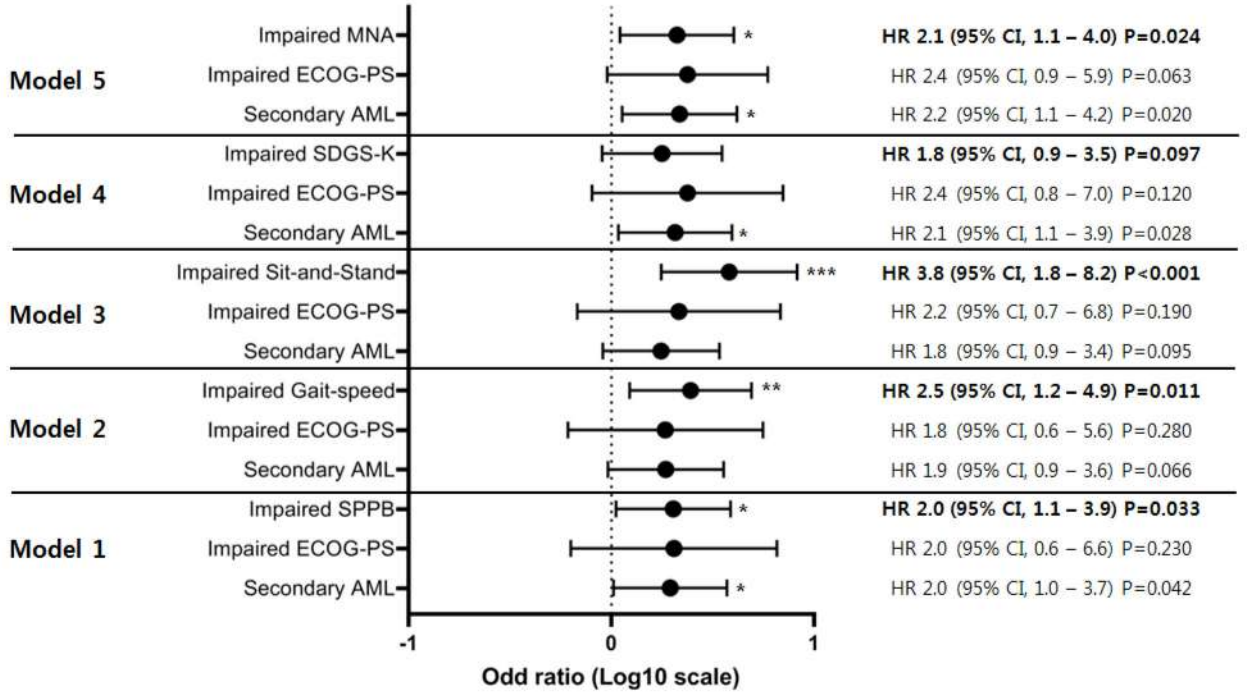
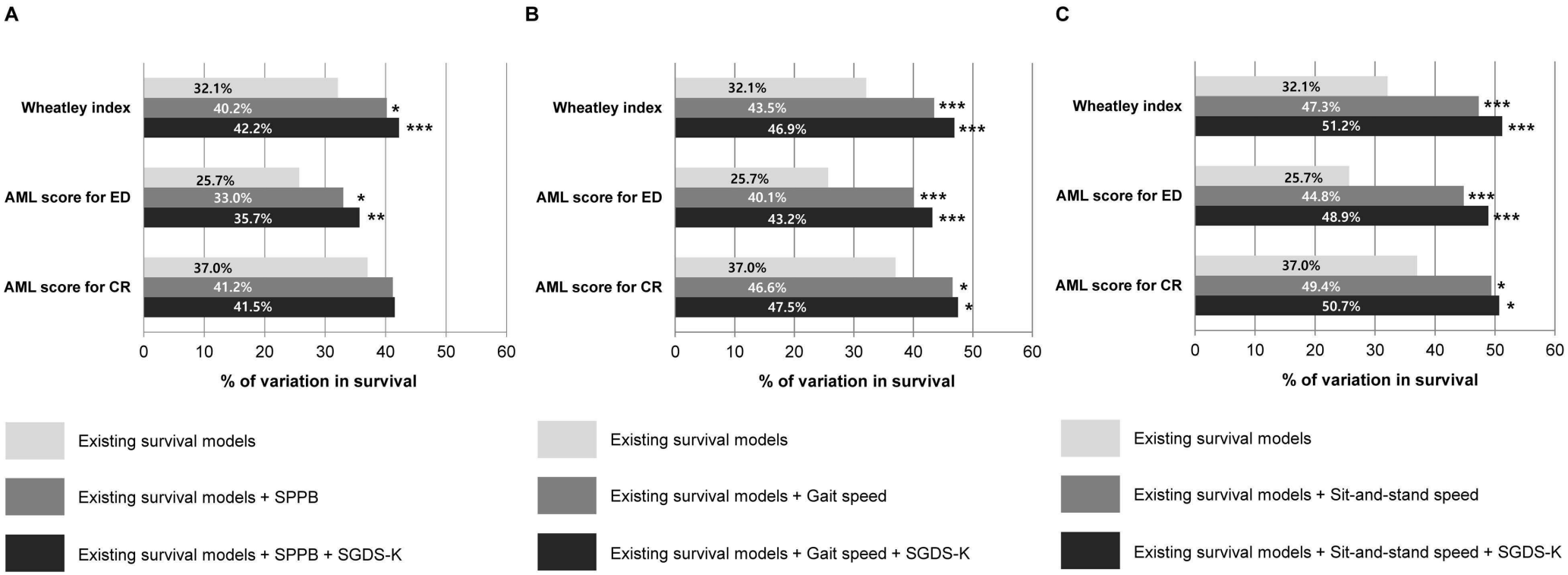


Figure 4


A
Wheatley index
32.1%
40.2%
42.2%
*
***
AML score for ED
25.7%
33.0%
35.7%
*
**
AML score for CR
37.0%
41.2%
41.5%
0 10 20 30 40 50 60
% of variation in survival
B
Wheatley index
32.1%
43.5%
46.9%
***
***
AML score for ED
25.7%
40.1%
43.2%
***
***
AML score for CR
37.0%
46.6%
47.5%
*
*
0 10 20 30 40 50 60
% of variation in survival
C
Wheatley index
32.1%
47.3%
51.2%
***
***
AML score for ED
25.7%
44.8%
48.9%
***
***
AML score for CR
37.0%
49.4%
50.7%
*
*
0 10 20 30 40 50 60
% of variation in survival
Existing survival models
Existing survival models + SPPB
Existing survival models + SPPB + SGDS-K
Existing survival models
Existing survival models + Gait speed
Existing survival models + Gait speed + SGDS-K
Existing survival models
Existing survival models + Sit-and-stand speed
Existing survival models + Sit-and-stand speed + SGDS-K