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Thai MDASI-AML/MDS in adults AML

RESEARCH ARTICLE

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Psychometric Properties of MD Anderson Symptoms Inventory for Acute Myeloid Leukemia Patients in Thailand

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Abstract

Background: The MD Anderson Symptoms Inventory for acute myeloid leukemia/myelodysplastic syndrome (MDASI-AML/MDS) is a specific patient-reported outcome measure (PROM) and widely used to assess the quality of life of acute myeloid leukemia (AML) patients. This study aimed to validate the inventory in Thai AML patients. **Methods:** After receiving permission, the original MDASI-AML/MDS was translated and cross-culturally adapted to Thai. Twenty AML patients were included in the study. Internal consistency was evaluated using Cronbach's alpha and test-retest reliability was analyzed using intraclass correlation coefficient (ICC). Spearman's rank correlation was used to investigate the subscales of Thai MDASI-AML/MDS and Thai version of European Quality of Life-5 Dimension-5 Level (Thai EQ-5D-5L). **Results:** All subscales of Thai MDASI-AML/MDS showed an acceptable Cronbach's alpha (0.64-0.91). The test-retest reliability of each subscale was adequate (ICC = 0.88-0.95). The core symptoms subscale in the Thai MDASI-AML/MDS strongly correlated to the anxiety/ depression subscale in the Thai EQ-5D-5L ($r = 0.69$, $p = 0.0006$). A strong correlation was demonstrated between the interference subscale of the Thai MDASI-AML/MDS and the usual activities subscale of Thai EQ-5D-5L ($r = 0.77$, $p = 0.0001$). A weak correlation was found between the MDS/AML specific symptoms subscale in the Thai MDASI-AML/MDS and anxiety and depression subscale in the Thai EQ-5D-5L ($r = 0.49$, $p = 0.0285$). The Thai MDASI-AML/MDS had strong correlation with Thai EQ-5D-5L ($r = 0.71$, $p = 0.0050$). **Conclusions:** The Thai MDASI-AML/MDS provides adequate internal consistency in all subscales as well as good construct validity and reliability for Thai patients.

Keywords: Thai MDASI-AML/MDS- Reliability- Validity- Psychometric properties

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Introduction

Acute myeloid leukemia (AML) is a diverse blood cancer, most commonly associated with bone marrow dysfunction and the production of high numbers of immature myeloid cells (Klepin et al., 2013; Saultz and Garzon, 2016).

AML is the most frequent acute leukemia in adults, with an annual incidence of 4.3 per 100,000 in the United States, with more than 60% of newly diagnosed patients over 60 years of age (Alibhai et al., 2009). AML patients also experience wide-ranging symptoms linked to cytopenia and blast proliferation, including malaise, bleeding, and infectious complications (Tamamyan et al., 2017), significantly impacting their health-related quality of life (HRQOL) (Buckley et al., 2018). The standard treatment for AML patients who are physically fit include high-intensity chemotherapy and consider allogeneic stem cell transplantation in some cases. In contrast, the elderly or unfit patients' treatment choices are low-intensity treatment, such as hypomethylating agents, low-dose chemotherapy, or supportive therapy, including red blood cells and/or platelet transfusions (De Kouchkovsky and Abdul-Hay, 2016). All of these therapeutic options also produce an additional symptom burden on AML patients.

Patient-reported outcome (PRO) is a term used for information about a patient's health condition, directly derived from the patients without any clinical expert's interference (Deshpande et al., 2011). Patient-reported outcome measures (PROMs) are proposed to measure the patient experience, for example, fatigue, symptom severity, impact on daily activities, and HRQOL (Bullinger and Quitmann, 2014).

The PROMs are crucial to the individualized treatment

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decisions and rapidly growing in healthcare systems and clinical studies. Many PROMs are tailored to measure the patient perspective in particular areas, for example, symptom-specific (e.g., pain, fatigue, and anxiety) and disease-specific instruments that are most relevant to a patient population.

The MD Anderson Symptoms Inventory for acute myeloid leukemia/ myelodysplastic syndrome (MDASI-AML/MDS) is one of the disease-specific PROMs for patients with AML or MDS. This questionnaire is a subjective assessment for symptoms burden and the impact of symptoms on daily functioning during the last 24 hours of treatment courses and showed good reliability and validity. The MDASI-AML/MDS was validated in AML and MDS patients in both inpatients and outpatients (Williams et al., 2013; Williams et al., 2015; Williams et al., 2018). There was no previous report on the study of AML-specific PROMs in the Thai version. MDASI-AML/MDS had not been linguistically and psychometrically validated in other versions except in English. This study aimed to create a Thai version of the original MDASI-AML/MDS, including translation and cross-cultural adaptation, and investigate the Thai version's psychometric properties, including reliability and validity.

Materials and Methods

This study is a cross-sectional descriptive design of Thai MDASI-AML/MDS's psychometric properties in AML patients during the treatment period between June 2020 to January 2021 in Chiang Mai University Hospital, Thailand. The inclusion criteria were adults AML patients aged 18 years or above who received the high-intensity chemotherapy or low-intensity treatment with the hypomethylating agent, used Thai as their first language, were able to read, understand, and complete the questionnaire without significant assistance. Patients who did not receive chemotherapy or hypomethylating agents with an active cerebral disorder or communication problems were excluded. We hypothesized that the Thai version could maintain the original version of MDASI-AML/MDS's reliability and validity. The local institutional research ethics committee approved this observational study.

The MDASI-AML/MDS Questionnaire

The MD Anderson Symptoms Inventory for acute myeloid leukemia/ myelodysplastic syndrome (MDASI-AML/MDS) is a disease site-specific module of patient-reported outcomes measurement consisting of three subscales, including 1) MDASI's 13 core symptoms (pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness/ tingling), 2) four symptom items specific to acute myeloid leukemia and myelodysplastic syndrome (feeling of malaise, diarrhea, muscle weakness and skin problems) and 3) six items of symptom interference with daily activities (general activity, mood, work, relations with others, walking and enjoyment of life). Patients rate the severity on a scale of 0 (symptom not present or no interference) to 10 (symptom severity as bad as you can imagine or complete interference) at their worst in the last 24 hours by themselves. The total score of the MDASI-AML/MDS reflects the symptom burden. It can be used in clinical practice for consistent routine symptom assessment and research to develop evidence for effective symptom management intervention. The reliability and validity of the MDASI-AML/MDS have already been investigated (Williams et al., 2013; Williams et al., 2015; Williams et al., 2018).

Translation and Cross-Cultural Adaptation

The authors requested permission from Williams et al., (2013), Williams et al., (2015) and Williams et al., (2018) to translate the original version into Thai. Translation and cross-cultural adaptation were performed. The forward translation by two bilingual translators (academic English language instructors from the Language Institute of Chiang Mai University) was independently translated from the original MDASI-AML/MDS into Thai versions. The backward translation into the English version was conducted by two bilingual English/Thai speakers (English language lecturers) to ensure that the original version's concepts were maintained.

Psychometric Testing of the Thai MDASI-AML/MDS

Internal consistency, test-retest reliability, and construct validity of the Thai MDASI-AML/MDS were evaluated. Internal consistency is the degree of correlation between items measuring the same outcomes. Cronbach's alpha was used to measure each subscale's internal consistency and the total score of Thai MDASI-AML/MDS. Values can be ranged from 0 to 1, with higher scores indicating more significant interrelatedness between items, and values of 0.70 or higher are considered to be adequate (Cronbach, 1946). Test-retest reliability is the ability of measurements to obtain similar results in a stable individual. The recommended time between the initial and the repeat administration of the measurement is two to seven days apart to avoid a recall and ensure that clinically significant change has not occurred. The Thai MDASI-AML/MDS was administered in two day intervals during the treatment period. The intraclass correlation coefficient (ICC), which ranges from 0 to 1, was 0.7 or above, indicating good reliability (Terwee et al., 2007). Construct validity measures the association between an instrument and theoretical hypotheses concerning the concepts being measured. The Thai EQ-5D-5L (Pattanaphesaj and Thavorncharoensap, 2015; Sakthong et al., 2015) was used to evaluate the construct validity of the concepts being measured in this study. Correlation among the Thai MDASI-AML/MDS subscales and Thai EQ-5D-5L was measured using Spearman's rank correlation coefficient (r). The degree of correlation was rated as weak ($r < 0.3$), moderate ($r = 0.3$-0.6), or strong ($r > 0.6$) (Hinkle DE, 1998).

Thai EQ-5D-5L

The EQ-5D-5L is a general symptom-specific PROM extensively used to evaluate health status in a

variety of illnesses (Herdman et al., 2011; Devlin and Brooks, 2017). The first part contains the five subscales: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each subscale has five levels of severity ranging from no problems to extreme problems. The second part uses numeric scales to evaluate general health conditions with scores ranging from 0 to 100. Higher scores indicate a better health status. The original version of EQ-5D-5L was translated into Thai, and its psychometric properties have been evaluated in many conditions (Pattanaphesaj and Thavorncharoensap, 2015; Sakthong et al., 2015).

Statistical Analysis

For the patients' characteristics, categorical variables are described as frequencies and percentages, and continuous variables are reported as means and standard deviations. The statistical significance was established at a p-value of 0.05 or less, and for multiple comparisons, the p-value was adjusted using Bonferroni's method. Following Hulley SB, et al. (Hulley SB, 2013) the estimated sample size calculation for correlation study used a correlation coefficient of 0.7 with an alpha error of 0.05 and a beta error of 0.10. A minimum sample size of 19 patients was projected when the anticipated dropout rate was 10%.

Results

Twenty evaluable acute myeloid leukemia patients were enrolled, the mean age of patients was 45.9 years (SD, 18.9 years), and eleven patients (55%) were female. Cytogenetics and mutational risk of AML were 10%, 60%, and 30% for favorable, intermediate, and unfavorable risk. Eight patients (40%) received the standard induction chemotherapy of

" 7+3 regimen " (seven-days of Cytarabine 100 mg/m^2 intravenous continuous infusion over 24 hours combined with three-days of Idarubicin 12 mg/m^2 bolus intravenously), five (25%) patients had been treated with intermediate-dose cytarabine consolidation chemotherapy (Cytarabine 1.5 g/m^2 slowly intravenous infused every 12 hours every other day for six doses) and hypomethylating agent (Azacytidine 75 mg/m^2 slowly intravenous drip for seven days) was curated to seven of the elderly AML patients (35%). The mean duration of hospitalization was 29.7 days (SD, 22.3 days), the mean time between diagnosis to first assessment was 27.6 days (SD, 19.9 days) and eight (40%) patients were in complete remission during the Thai MDASI-AML/MDS and Thai EQ-5D-5L assessment (Table 1).

Table 1. Baseline Characteristics of AML Patients received the Thai MDASI-AML/MDS assessment (n=20)

Baseline characteristics	N = 20
Female, n (%)	11 (55)
Age, mean ± SD	45.9 ± 18.9 years
< 40 years, n (%)	9 (45)
40-60 years, n (%)	6 (30)
> 60 years, n (%)	5 (25)
AML risk classification	
Favorable, n (%)	2 (10)
Intermediate, n (%)	12 (60)
Unfavorable, n (%)	6 (30)
Treatment	
Induction: 7+3 regimen, n (%)	8 (40)
Consolidation: Intermediate-dose Cytarabine, n (%)	5 (25)
Hypomethylating agents: Azacytidine, n (%)	7 (35)
Hospitalization, mean ± SD	29.7 ± 22.3 days
≤ 30 days, n (%)	13 (65)
> 30 days, n (%)	7 (35)
Duration between diagnosis to assessment, mean ± SD	27.6 ± 19.9 days
Disease status	
Complete remission, n (%)	8 (40)
Relapse or refractory, n (%)	2 (10)
Pending for disease evaluation, n (%)	10 (50)

Table 2. Cronbach's Alpha for Each Subscale in the Thai MDASI-AML/MDS (n=20)

Subscale	Cronbach's alpha	
	First time	Second time
13-core symptoms	0.86	0.89
4-specific symptoms to AML/MDS	0.64	0.71
6-interferences	0.83	0.84
Thai MDASI-AML/MDS	0.86	0.91

Internal Consistency and Test-Retest Reliability

The internal consistency of the Thai MDASI-AML/MDS was assessed with 20 patients (Table 2). All subscales had adequate internal consistency. Most subscales (13-core symptoms and 6-interferences) demonstrated high Cronbach's alpha values ranging from 0.84 to 0.89, while the four specific symptoms to the AML/MDS subscale

Table 3. Test-Retest Reliability of the Thai MDASI-AML/MDS (n=20)

Subscale	Baseline	Retest	ICC (95% confidence interval)
	Mean ± SD	Mean ± SD	
13-core symptoms	24.80 ± 16.70	22.81 ± 16.63	0.94 (0.85-0.98)
4-specific symptoms to AML/MDS	7.35 ± 5.13	6.54 ± 5.54	0.88 (0.70-0.95)
6-interferences	20.28 ± 12.57	19.15 ± 12.44	0.95 (0.89-0.98)
Thai MDASI-AML/MDS	52.15 ± 26.82	49.45 ± 30.92	0.94 (0.85-0.98)

Table 4. Spearman's Correlation for Each Subscale Among the Thai MDASI-AML/MDS and Thai EQ-5D-5L (n=20)

Thai EQ-5D-5L	Mobility	Self-Care activities	Usual activities	Pain and discomfort	Anxiety and depression	Total score
Thai MDASI-AML/MDS						
13-core symptoms	0.19	0.19	0.61*	0.55*	0.69*	0.48*
4-specific symptoms to AML/MDS	0.24	0.21	0.67*	0.51*	0.49*	0.56*
6-interferences	0.52*	0.26	0.77*	0.49*	0.73*	0.73*
Total score	0.20	0.25	0.75*	0.54*	0.70*	0.71*

* Statistically significant (p-value < 0.05) adjusted for multiple comparison using Bonferroni's method

presented slightly lower Cronbach's alpha values (0.64 to 0.71). However, the total Thai MDASI-AML/MDS score showed the highest internal consistency (Cronbach's alpha of 0.86 to 0.91). Test-retest reliability was performed in all patients, and all subscales had good reliability with intraclass correlation coefficient (ICC) values between 0.88 and 0.95 (Table 3).

Construct Validity

The evaluation of construct validity of the Thai MDASI-AML/MDS was conducted in all patients. The correlation among subscales for the Thai MDASI-AML/MDS and the Thai EQ-5D-5L was compared (Table 4). The 13-core symptoms subscale in the Thai MDASI-AML/MDS showed the correlation with the usual activities subscale (r = 0.61, p = 0.0096), the pain and discomfort subscale (r = 0.55, p = 0.0222) and the anxiety/depression subscale (r = 0.69, p = 0.0006) in the Thai EQ-5D-5L. The four-MDS/AML specific symptoms subscale in the Thai MDASI-AML/MDS correlated to the Thai EQ-5D-5L subscale of usual activities (r = 0.67, p = 0.0011), pain and discomfort (r = 0.51, p = 0.0216) as well as anxiety and depression (r = 0.49, p = 0.0285). The strong correlation was demonstrated between the six-interferences subscale of the Thai MDASI-AML/MDS and the usual activities subscale of Thai EQ-5D-5L (r = 0.77, p = 0.0001), together with the anxiety and depression (r = 0.73, p = 0.0002) but moderate correlation has been showed to mobility (r = 0.52, p = 0.0198) and pain and discomfort (r = 0.49, p = 0.0298) subscale. All of the Thai MDASI-AML/MDS subscales were significantly correlated to the total score of the Thai EQ-5D-5L. There was the strong correlation between Thai MDASI-AML/MDS and Thai EQ-5D-5L (r = 0.71, p = 0.0050).

Discussion

This study demonstrated the reliability and validity assessment of the Thai version of MDASI-AML/MDS in acute myeloid leukemia patients who currently received treatment with a mean duration of hospitalization of 29.7 days (SD, 22.3 days) and mean time between diagnosis to the first assessment of 27.6 days (SD, 19.9 days). The overall internal consistency was relatively good in most of the subscales (Cronbach's alpha of 0.83 to 0.89 for 13-core symptoms as well as 6-interferences, and 0.64 to 0.71 for AML/MDS specific symptoms subscale) with decent test-retest reliability (intraclass correlation coefficient (ICC) values of 0.88 to 0.95).

For construct validity evaluation by compared each of subscale to Thai EQ-5D-5L, Thai MDASI-AML/MDS showed the moderate to strong correlation between the 13-core symptoms subscale with the usual activities subscale (r = 0.61, p = 0.0096), the pain and discomfort subscale (r = 0.55, p = 0.0222) and the anxiety/depression subscale (r = 0.69, p = 0.0006) in the Thai EQ-5D-5L. The six-interferences subscale of the Thai MDASI-AML/MDS established strong correlation to the usual activities' subscale (r = 0.77, p = 0.0001), and the anxiety and depression (r = 0.73, p = 0.0002) of Thai EQ-5D-5L.

Overall, Thai MDASI-AML/MDS also had strong correlation to the Thai EQ-5D-5L (r = 0.71, p = 0.0050). The health-related quality of life (HRQOL) assessment via patient-reported outcomes measurements (PROMs) is vital to fully understand treatment benefits and disease burden, especially in the poor clinical prognosis diseases such as patients with acute myeloid leukemia. Additional studies should be considered to explore how systematic the assessment of patient perspective is, not only in the context of a clinical trial but in the context of real-world clinical practice, to support the discussion with patients and inform treatment decision-making. The systematic review and meta-analysis study of PROMs in patients with AML and MDS revealed the various kinds of quality-of-life instruments were used in the published and ongoing clinical trials (Stauder et al., 2020). The most frequently used were EORTC QLQ-C30 for cancer-specific as well as SF-36 for general assessment, and also addressed that the AML specific instruments for HRQOL assessment (FACT-Leu, EORTC QLQ-Leu, MDASI-AML/MDS) were undervalued as the minority of published studies and MDASI-AML/MDS accounted to only four studies from 172 AML publications (Stauder et al., 2020).

This study performed the psychometric properties analysis of Thai MDASI-AML/MDS to expand the utility of AML specific quality of life instrument. Moreover, there has been an increase up to 85% of oncology trials between 2006 to 2012 to disclose the inclusion of PROMs to address an endpoint evaluating HRQOL on ClinicalTrials.gov (provided by the United State National Library of Medicine) by documenting the patient's perspective, and the importance of AML specific PROMs is highly selective for the EMA and US-FDA drug approval for new further therapeutic agents (Zagadailov et al., 2013). Although several PROMs have been validated, there was a lack of evidence supporting the selected instruments' appropriateness, and more research is needed to determine the most clinically useful instruments in AML patients

(DeMuro et al., 2012; Salas et al., 2020).

This study was the first report of translation and cross-cultural adaptation into a Thai version of MDASI-AML/MDS. Adequate construct validity was revealed compared to the Thai EQ-5D-5L. However, some of the limitations in this study should be addressed. Firstly, the weak correlation of the mobility and self-care activities subscale of the Thai EQ-5D-5L to all subscales of Thai MDASI-AML/MDS. This could be interpreted that EQ-5D-5L and MDASI-AML/MDS measure HRQOL in different aspects within a similar domain, so the two instruments' results could not be directly compared. Although the MDASI-AML/MDS was not frequently used in the previously published studies of AML and lack of vigorous testing for their psychometric properties, this study deserved to determine AML-specific PROM values in the context of real-life clinical practice. The small scale of this study with a relatively heterogenous status of AML patients may affect the results, the Thai MDASI-AML/MDS's psychometric properties showed adequate internal consistency, good reliability, and validity, same as the original version of MDASI-AML/MDS (Williams et al., 2013; Williams et al., 2015; Williams et al., 2018). Furthermore, a larger magnitude of the study population to validate MDASI-AML/MDS in other languages during the varied stages of AML treatment is highly warranted. In conclusion, the Thai MDASI-AML/MDS provides adequate internal consistency in all subscales and reliability and good construct validity for assessing Thai AML patients who were receiving the treatment in various kinds of therapy. The Thai MDASI-AML/MDS is a patient-rated outcome measurement available for clinicians and researchers to evaluate the symptoms burden in both clinical practice and medical research.

Author Contribution Statement

Conceptualization: Thanawat Rattanathammethee, Chatree Chai-Adisaksopha; Data curation: Thanawat Rattanathammethee, Omjai Wongkhut; Formal analysis: Thanawat Rattanathammethee, Omjai Wongkhut; Investigation: Thanawat Rattanathammethee, Omjai Wongkhut; Methodology: Thanawat Rattanathammethee, Chatree Chai-Adisaksopha; Writing - original draft: Thanawat Rattanathammethee, Omjai Wongkhut; Writing - review and editing: All of the authors.

Ethics Approval

This study was approved by the institutional research board (Research Ethics Committee 4), Faculty of Medicine, Chiang Mai University, Thailand. All procedures were conducted following the ethical standards of the responsible committees on human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2008.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Approval body of the research

This research was approved as a part of residency training program of the Thai board of Internal Medicine, the royal college of physician in Thailand.

Completing Interests

All the authors declare no competing interests.

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