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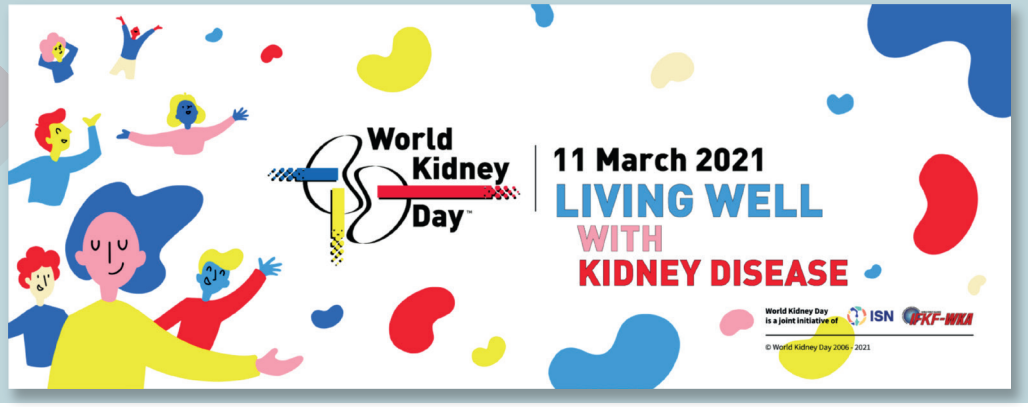

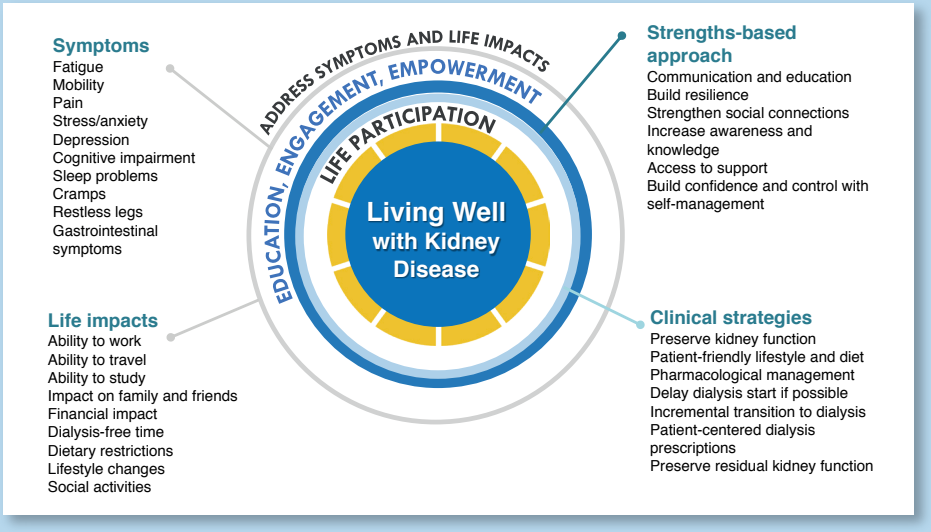

By Kamyar Kalantar-Zadeh, et al.

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The Increasing Risk of Dementia in Psoriasis: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: To systemically summarize and meta-analyze the risk of dementia in psoriasis patients.

Methods: A systematic review was performed in two databases (EMBASE and MEDLINE). The eligible studies had to be a cohort study or a cross-sectional study that compared either the prevalence or incidence of dementia in psoriatic patients, versus comparators without psoriasis.

Results: Of 791 retrieved articles, seven studies met the inclusion criteria and were included into this systematic review and meta-analysis. The risk of incident and prevalent dementia were significantly higher in psoriatic patients, with a pooled risk ratio of 1.16 (95% CI: 1.02-1.33; I^2 96%) and 1.36 (95% CI: 1.07-1.72; I^2 10%), respectively.

Conclusion: This study revealed a slight increase in both the incidence and prevalence of dementia in psoriasis patients. However, dermatologists should carefully observe and periodically screen psoriasis patients for this comorbidity, especially among those who have symptoms and signs of cognitive impairment.

Keywords: Psoriasis; dementia; cognitive impairment; Alzheimer's disease; comorbidities (Siriraj Med J 2021; 73: 145-154)

INTRODUCTION

Psoriasis is a chronic auto-inflammatory skin disease which affects 0.9-8.5% of the population worldwide.[1] Genetic and environmental factors that activate the immune system play a crucial role in the pathogenesis of psoriasis. The activation of the innate and adaptive immunity resulting in the production of several inflammatory cytokines, such as tumor necrosis factors, interleukin (IL) -12, IL-23, and IL-17, are driven keys in the development of psoriasis and comorbid diseases. Multiple comorbidities have been reported to be associated with psoriasis, such as metabolic syndrome, diabetes mellitus, non-alcoholic steatohepatitis, uveitis, and inflammatory bowel disease.[2,3]

Dementia is an acquired disorder characterized by a significant decline in cognition involving at least one cognitive domains. These domains include complex attention, executive function, learning and memory, language, perceptual–motor/visuospatial function, and social cognition. This impairment is severe enough to interfere with patients' daily-life functions. The incidence of dementia globally increased due to the aging population in combination with the growing awareness of this disease.[4] Dementia can be categorized into two groups depending on the causation and pathophysiology: neurodegenerative and non-neurodegenerative causes. Examples of neurodegenerative dementia are Alzheimer's disease; dementia with lewy bodies; and frontotemporal lobar degeneration, whereas vascular dementia is an example of a non-neurodegenerative dementia. Both neurodegenerative and non-neurodegenerative causes

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can occur in the same patient with dementia.[5] Among the causes of dementia, Alzheimer's disease is the majority of overall cases (60-80%).[6,7]

Previous systematic review and meta-analysis studies have reported the relationship between psoriasis and some neurological disorders, such as multiple sclerosis, stroke and Parkinson's disease.[8,9] However, data regarding the dementia risk in patients with psoriasis are conflicting. Some studies have pointed out this risk, while others have revealed the negative association.[10-12] Our study aims to systematically summarize and meta-analyze the risk of dementia in psoriatic patients.

MATERIALS AND METHODS

Search strategy

Two investigators (C.C. and L.C.) had individually conducted a systematic review by searching published studies in the MEDLINE and EMBASE databases, from inception to February, 2020. The search terms included "psoriasis," "dementia," and related terms, as described in Table S1. Eligible studies could be a cohort study or a cross-sectional study that consisted of one psoriatic patients group and another without psoriasis and reported prevalence or incidence of dementia in both groups. Then, the difference in prevalence or incidence of dementia were recorded as a relative-risk ratio (RR), an odds ratio (OR), a hazard-risk ratio (HR), an incidence-rate ratio (IRR), or a standardized-incidence ratio (SIR), with an associated 95% confidence interval (CI). If those ratios were not available, sufficient primary data to analyze them was acceptable. Exclusion criterion was non- English published articles.

The title and abstract of the obtained articles were individually reviewed by the two aforementioned authors. Articles that obviously did not meet our inclusion criteria were excluded in the first stage. Two authors reviewed the remaining potentially qualified full-text studies independently. Any disagreement was resolved via discussion between the two authors. The Newcastle–Ottawa quality-assessment scale was used for a quality assessment of the included studies.[13]

Data extraction

The data was retrieved and collected from those studies. The collected data included the first author's name, the publication year, the journal's title, the title of the study, the study's sites, the study type, the step approach to diagnose psoriasis and dementia, the enrollment method involving patients with psoriasis and comparators, the demographic data of patients with psoriasis and comparators, the follow-up period, the confounder adjusted in multivariate analysis, and the adjusted-effect estimates, with a 95% confidence interval (CI). Data extraction was independently performed by two authors.

Statistical analysis

Statistical analysis was analyzed by using Review Manager 5.3 software from the Cochrane Collaboration (London, UK). The generic-inverse variance method of DerSimonian and Laird was used to pool the effect estimate of each study together.[14] A random-effect model was preferred because the postulation behind the fixed-effect model that the same result would be obtained from every study is almost always not true. Cochran's *Q* test and I^2 statistic were used to assess for between-study statistical heterogeneity.[15] Publication bias was determined by funnel plot.

RESULTS

A total of 791 potentially qualified studies from the EMBASE and MEDLINE databases were identified. We excluded 53 duplicated articles, and then 738 articles underwent the first round of title and abstract screening. At this stage, 711 articles were excluded because they obviously did not meet the inclusion criteria based on the type of article or the study's design. Twenty-seven studies were qualified for a full-text review. Twenty of these studies were excluded for the following reasons: did not report an outcome of interest (n=12); descriptive study (n=3), a review (n=3), duplicated database (n=1), and not published in English (n=1). The remaining seven studies were finally included in the meta-analysis.

Of these seven studies, five compared the incidence of dementia between the groups, while two compared the prevalence of dementia. The flowchart demonstrating the literature review and selection process of this study is shown as Fig 1. The methodology and the characteristics of the participants of the incidence and prevalence of dementia studies, as well as the Newcastle–Ottawa quality-assessment scale, are described. (Tables 1 and 2)

Risk of incident dementia

Of the five eligible studies, 553,733 psoriasis patients and 2,845,260 comparators without psoriasis were analyzed in the meta-analysis.[10-12,16,17] It should be noted that one study did not reveal the number of participants.[12] The dementia risk in psoriatic patients was significantly higher, compared to comparators without psoriasis, with a pooled risk ratio of 1.16 (95% CI: 1.02-1.33). There was a high heterogeneity (I^2=96%) in this analysis. (Fig 2). The funnel plot was relatively symmetric (Fig 3).

TABLE S1. Database search strategy

Search strategy Database
MEDLINE
1. psoriasis.mp. OR exp Psoriasis/
2. dementia.mp OR exp Dementia/ OR exp Frontotemporal dementia/ OR exp Dementia, Vascular/ OR exp Dementia, Multi-Infarct/
3. Alzheimer.mp OR exp Alzheimer Disease OR exp Cognitive Dysfunction/
4. 2 OR 3
5. 1 AND 4
EMBASE
1. 'psoriasis'/exp OR 'psoriasis'
2. 'dementia'/exp OR 'dementia'
3. 'frontotemporal dementia'/exp OR 'frontotemporal dementia'
4. 'multiinfarct dementia'/exp OR 'multiinfarct dementia'
5. 'alzheimer disease'/exp OR 'alzheimer disease'
6. 'cognitive defect'/exp OR 'cognitive defect'
7. 2 OR 3 OR 4 OR 5 OR 6
8. 1 AND 7

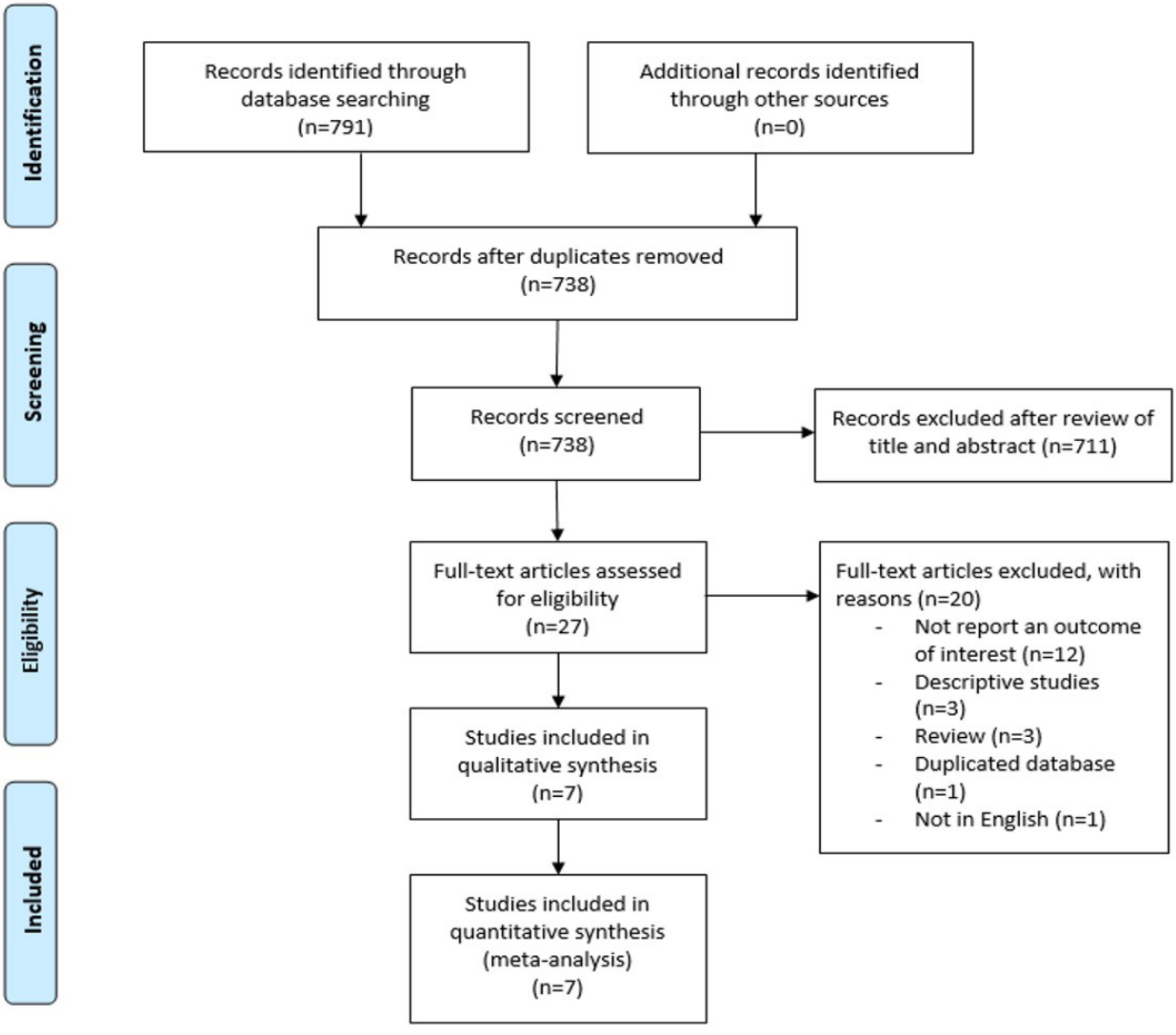

Fig 1. Flow chart describing the literature review and selection process

TABLE 1. Characteristics of included incident studies

	Wotton, *et al.*	**Pezzolo, *et al.***	**Kim, *et al.***	**Huang, *et al.***	**Leisner, *et al.***
Country of origin	United Kingdom	Netherlands	Republic of Korea	Taiwan	Denmark
Study design	Retrospective cohort study	Cohort study	Cohort study	Retrospective cohort study	Cohort study
Year of publication	2017	2018	2019	2019	2019
Cases	Cases of psoriasis were identified from the data set of English national Hospital Episode Statistics during April 1, 1998 to March 31, 2012. This data included all hospital admissions (including day cases) in all National Health Service (NHS) hospitals in England Diagnosis of psoriasis was based on presence of diagnostic codes of psoriasis for the first time of day case care or inpatient admission on the hospital discharge abstract during the study period.	Cases of psoriasis were identified from the prospective population-based Rotterdam Study (RS). The original cohort was started in 1990 and extended in 2000 and 2005. Participants have been followed up and examined every 4 years. Psoriasis participants were initially identified by a diagnostic code and a record of psoriasis medication. Definite cases of psoriasis were (i) patients with a diagnosis of psoriasis by a dermatologist or rheumatologist, (ii) patients whose disease was diagnosed twice or more by the general practitioner, (iii) patients with psoriasis-specific medications, and (iv) patients with a diagnosis of psoriasis at the time of skin examination	Cases of psoriasis were identified from the Korean National Health Insurance System Database during 2008-2014 Diagnosis of psoriasis was defined as having at least 3 physical examinations.	Cases of psoriasis were identified from the National Health Insurance Research Database (NHIRD) during January 1, 1996 to December 31, 2013. This registry covers over 99.0% of the citizens in Taiwan Diagnosis of psoriasis was defined as having at least 1 inpatient or 3 outpatient diagnoses of psoriasis on the basis of diagnostic code given by a rheumatologist or dermatologist. Individual younger than 40 and diagnosis of dementia before psoriasis were excluded.	Cases of psoriasis were identified from population-based registries covering all Danish hospitals who was born from 1900-1995 Diagnosis of psoriasis was defined as having at least 2 hospital or outpatient-based diagnoses of psoriasis from January 1, 1977 to January 1, 2012.

TABLE 1. Characteristics of included incident studies (Continue)

	Wotton, *et al.*	**Pezzolo, *et al.***	**Kim, *et al.***	**Huang, *et al.***	**Leisner, *et al.***
Country of origin	United Kingdom	Netherlands	Republic of Korea	Taiwan	Denmark
Study design	Retrospective cohort study	Cohort study	Cohort study	Retrospective cohort study	Cohort study
Comparators	Individuals with other medical and surgical conditions as the primary discharge diagnoses in the first admission.	Individuals without a psoriasis diagnosis or anti-psoriatic medication, with a comparable age and gender distribution	Gender and age-matched controls without psoriasis	Gender, age, level of urbanization of residence, index date-matched comparators without psoriasis	Gender and age-matched comparators without psoriasis
Diagnosis of incident dementia	Presence of diagnostic code for dementia in any subsequent NHS hospital care, or death from dementia Codes for dementia secondary to other conditions were excluded.	Standard diagnostic criteria for dementia and Alzheimer's disease was used. The final diagnosis was made by a consensus panel led by a neurologist.	-	Presence of diagnostic code for dementia at least 1 inpatient or 3 outpatient recorded.	Presence of diagnostic code for dementia
Number of subjects (cases/comparators)	-	311 / 9305	535,927 / 2,679,635	3,820 / 15,280	13,675 / 141,040
Percentage of female (cases/comparators)	44.7 / -	-	-	36.4 / 36.4	49.6/49.5
Mean age in years (cases/comparators)	56.5 / -	-	-	57.6 / -	-
Follow-up	Until first dementia admission	Started between 2002-2005 and followed until diagnosis of dementia, death, lost to follow up or end of the study at January 1, 2015	-	Until first diagnosis of dementia, withdrawal, or the end of 2013	Until diagnoses of a mental disorder, death, emigration or end of the study (January 1, 2013)

TABLE 1. Characteristics of included incident studies (Continue)

	Wotton, *et al.*	**Pezzolo, *et al.***	**Kim, *et al.***	**Huang, *et al.***	**Leisner, *et al.***
Country of origin	United Kingdom	Netherlands	Republic of Korea	Taiwan	Denmark
Study design	Retrospective cohort study	Cohort study	Cohort study	Retrospective cohort study	Cohort study
Confounder assessed in the multivariate analysis	Age (in 5-year bands), gender, time period in single calendar year, region of residence and quintile of patients' Index of Deprivation score	Age, gender, education, and cardiovascular risk factor	-	Age, gender, level of urbanization of residence, hypertension, heart disease, diabetes, hyperlipidemia, stroke and depression	Age, gender
Quality assessment	Selection: 4 Comparability: 2 Outcome: 3	Selection: 3 Comparability: 2 Outcome: 2	Selection: 3 Comparability: 1 Outcome: 2	Selection: 4 Comparability: 2 Outcome: 2	Selection: 4 Comparability: 1 Outcome: 2

TABLE 2. Characteristics of included prevalent studies

	Feldman, *et al.*	Mitchell, *et al.*
Country of origin	United States	United States
Study design	Cross-sectional study	Cross-sectional study
Year of publication	2015	2018
Cases	Cases of adult psoriasis (aged 18-64 years) were identified from the OptumHealth Reporting and Insights claims database from January 1, 2007 to March 31, 2012 Cases were patients with at least 2 diagnostic codes of psoriasis on different dates. Moderate to severe psoriasis was defined as those receiving at least 1 systemic therapy or phototherapy during the study period.	Cases of adult psoriasis (aged 40-89 years) were identified by searching a medical record data repository (>5 million patients) from January 2001 to November 2017. Diagnosis of psoriasis was based on a presence of diagnostic codes of psoriasis
Comparators	Comparators were gender, age and geographic matched-individuals without diagnostic code of psoriasis and psoriatic arthritis	Comparators were the rest of patients with no diagnosis of psoriasis
Diagnosis of prevalent dementia	Presence of diagnostic code in either the primary or secondary diagnosis	Presence of diagnostic code of dementia
Number of subjects (cases/comparators)	5492 / 5492	5825 / 151,320
Percentage of female gender (cases/comparators)	44.5 / 44.5	-
Mean age in years (cases/comparators)	47.6 / 47.6	-
Confounder assessed in multivariate analysis	Demographics, index year, insurance type, and other comorbidities	Age, gender, race
Quality assessment (Newcastle-Ottawa scale)	Selection: 4 Comparability: 2 Exposure: 3	Selection: 4 Comparability: 2 Exposure: 3

Risk of prevalent dementia

A total of 11,317 psoriatic patients and 156,812 comparators without psoriasis were included in the analysis of prevalent dementia.[18,19] There was a significantly higher risk of dementia in the psoriasis group, compared to non-psoriatic individuals, with a pooled risk ratio of 1.36 (95% CI: 1.07-1.72). The statistical heterogeneity was insignificant (I^2=10%) (Fig 4). Number of studies were not enough to create a funnel plot for this prevalent analysis.

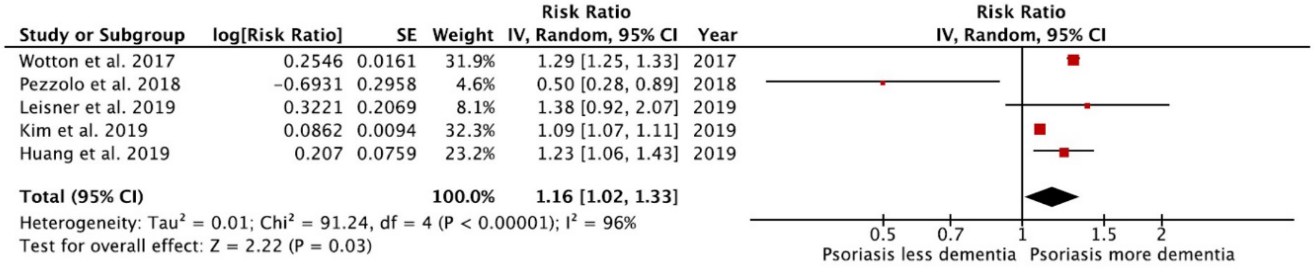

Fig 2. Forest plot of risk of incident dementia

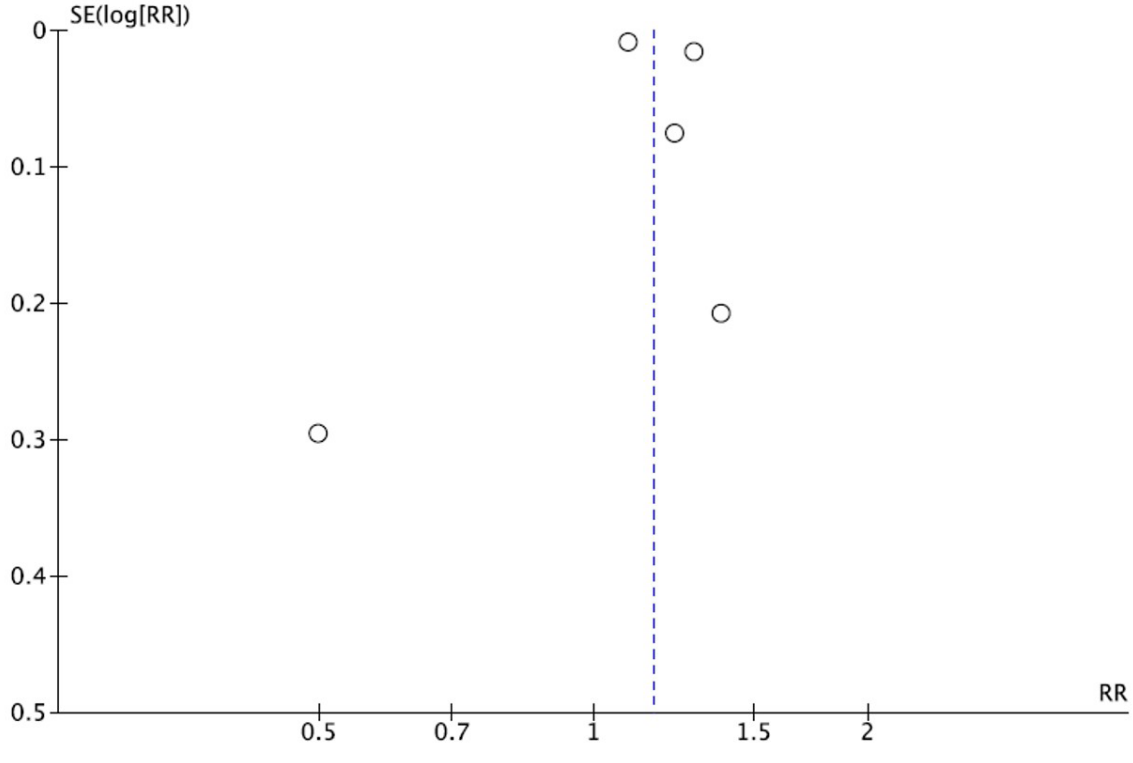

Fig 3. Funnel plot of incident dementia

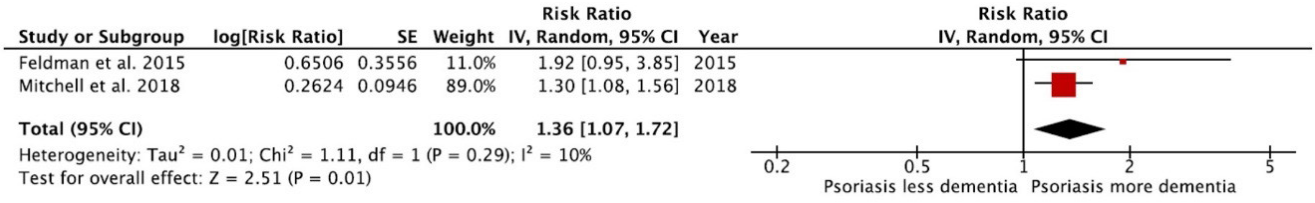

Fig 4. Forest plot of risk of prevalent dementia

DISCUSSION

This study combined all of the available data regarding the relationship between psoriasis and dementia. The pooled analyses found that both the incidence and prevalence of dementia were significantly higher among psoriatic patients than in the general population.

Dementia is a global medical problem. Its prevalence ranges from 1% to 5% at the age of 65 years, and increases substantially to approximately 30% at age 80.[20] Given the aging population worldwide, dementia is considered a major health problem, with an enormous impact on people's quality of life, as well as on the health system financially. The World Health Organization has established dementia as a global health priority to raise awareness of this disease.[21]

There are several known risk factors for dementia. First, genetic factor, especially Apolipoprotein E polymorphism on Chromosome 19, is one of the well-established predisposing factors for Alzheimer's disease.[22] Second, lifestyle factors, such as smoking or heavy consumption of alcohol, have been reported to increase the risk of dementia. Moreover, an increased risk of dementia has been found in association with several comorbidities, such as heart disease, hypertension, and psychiatric illness.[4]

The current study found a significant association between psoriasis and dementia. The mechanism behind the increased risk of dementia among psoriatic patients is not known with certainty, but is probably linked to inflammation. Psoriasis is a chronic inflammatory disease, and the role of inflammation in the pathogenesis of dementia has been reported. Numerous studies have found that several pro-inflammatory mediators involved in the pathogenesis of psoriasis[23], such as tumor necrosis factor α, IL-1, IL-6, and C-reactive protein, are upregulated in patients with dementia.[24,25] These inflammatory mediators can trigger the neuroinflammation process, resulting in microglial stimulation, a release of pro-inflammatory cytokines, and neuronal injury,[26] which can ultimately lead to a decrease in brain capability and neuroplasticity deficits.[27] In fact, one of the included studies also found that systemic treatments for psoriasis to reduce systemic inflammation can significantly reduce the risk of dementia, compared with no such treatment.[16]

The other possible explanation is genetic predisposition as the genetic polymorphism of Apolipoprotein E, which is a well-known risk factor in Alzheimer's disease, is also associated with the risk of psoriasis.[28]

Some limitations of the current study should be noted. First, the meta-analysis of incident dementia revealed high heterogeneity, which may suggest that those studies were somewhat too different to combine. Secondly, some of the included studies were of low quality, as is evident from their low Newcastle-Ottawa scores. Lastly, there is a lack of detail in some included studies, as they were published only as conference abstracts.

CONCLUSION

In conclusion, this study revealed a slight increase of both the incidence and prevalence of dementia in psoriasis patients. Further studies are needed to confirm this association. Dermatologists should carefully observe and periodically screen psoriasis patients for this comorbidity, especially people those who have symptoms and signs of cognitive impairment, in order to provide them with the best care.

Conflict-of-interest statement: All authors have no conflicts of interest and no financial support to declare.

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Delirium in a Medical Intensive Care Unit: Prevalence, Risk Factors and Outcomes

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ABSTRACT

Objective: Delirium is a common problem in critical care. Its prevalence in the unit varies, depending upon the severity of the illness and the diagnostic methods. Currently, the CAM-ICU is a diagnostic tool with good diagnostic accuracy. Our study aimed to determine the prevalence, associated factors, and outcomes of delirium in our unit by using the CAM-ICU.

Methods: Our prospective cohort study included all patients admitted to the hospital's medical ICU from August to December, 2013. Patients with psychosis and/or in a coma (RAAS<-3) were excluded. We assessed delirium by using the CAM-ICU within the first 24 hours of admission and then serially, every 48 hours until discharge. Factors associated with this condition and patients' outcomes were also explored.

Results: A total of 74 patients were included. Of these, 43% were male, 40% had sepsis, and 81% were mechanically ventilated. Twenty-eight patients (38%) had delirium upon admission. The delirium patients were older and had a higher percentage of dementia. Univariate analysis revealed that dementia, anemia, acute metabolic acidosis, and the use of mechanical ventilation were associated with the occurrence of delirium, and, for age > 70 years, anemia and metabolic acidosis remained significant on multivariate analysis. Delirium was significantly associated with prolonged hospitalization (>30 days), with OR = 4.84 (p=0.009), and with increased mortality, with OR = 25.0 (p=0.001).

Conclusion: This study confirmed that delirium was common in the medical ICU and was associated with poor outcomes. Importantly, associated factors with delirium in our study appeared to be modifiable. Further study on early management and prevention of those risk factors is crucial.

Keywords: Delirium; critically ill patients; CAM-ICU (Siriraj Med J 2021; 73: 155-160)

INTRODUCTION

Delirium is a syndrome of acute brain dysfunction defined as a disturbance in attention and awareness from the baseline. Changes in cognition not better accounted for by a preexisting, established, or evolving dementia occurs in this setting. The condition develops over a short period and fluctuates in severity during the course of a day.[1] Many terms have been used to describe this condition: intensive care unit (ICU) psychosis, postoperative delirium, and ICU syndrome.[2,3] Delirium should be differentiated from dementia, major depression, and psychogenic illness. Studies have revealed that ICU delirium was associated with poor clinical outcomes, such as a prolonged length of hospital stay, functional and cognitive decline, and increases in mortality and morbidity.[4-6] A systemic review in medical wards demonstrated that delirium was associated with increased mortality at discharge and at 12 months, as well as with an increased length of hospital stay. Persistent symptoms of delirium might be found at discharge and at 6 to 12 months thereafter.[7]

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The prevalence of delirium has varied among the studies. In the hospital setting, it has ranged from 6-56%[8]; in post-operative surgical ICUs, it has ranged from 15-53%; and in medical-surgical ICUs, from 20-80%.[9-11] This has depended on the severity of illness and the diagnostic method.[12] The prevalence of delirium in elderly patients in our institution was 48%. Those who had this condition had a longer length of stay and an increased in-hospital mortality[13] than others.

There are certain difficulties in the diagnosis of ICU delirium, especially regarding mechanically ventilated patients. As a result, many scoring systems have been developed. Examples include the Confusion Assessment Method for the ICU (CAM-ICU); the Nursing Delirium Screening Scale (Nu-DESC); and the Delirium Detection Score (DDS). Among these, the CAM-ICU has had the highest validity,[14] with sensitivities of 95-100%, specificities of 89-93%, and a high inter-rater reliability.[15] The CAM-ICU has been translated into Thai.[16] It has been back-translated, reviewed, and validated.[17] The results have revealed a sensitivity of 92.33%, a specificity of 94.7%, and high inter-rater reliability (Cohen's kappa = 0.82; p-value < 0.001). Our study primarily aimed to determine the prevalence of delirium in our unit by using the Thai CAM-ICU. The secondary objectives were to assess associating factors, including the outcomes of this condition.

MATERIALS AND METHODS

Study design

This prospective cohort study included all patients who were admitted to the Medical ICUs at Siriraj Hospital in Bangkok from August to December, 2013. Exclusion criteria included psychosis, coma (The Richmond Agitation and Sedation Scale, RASS<-3), aphasia and being unable to Thai language communication. Our unit is a 16 beds facility a tertiary care unit with nurse to patient ratio 1:1 during day time and 1:2 at night. During the study period, there was no standard protocol for sedatives and analgesic agents usage available in our ICU. The decision to prescribe sedatives and analgesic agents were depended on the attending physician judgment.

Delirium Assessment

All patients were screened for delirium using the CAM-ICU (Thai version). Delirium assessments were undertaken within the first 24 hours of admission and serially every 48 hours until discharge or death. One of the authors (W.J.) was the assessor of delirium.

The recorded patient characteristics including age, sex, alcohol consumption, history of dementia, history of delirium, and basic activities of daily living (ADL). The APACHE-II illness score and the Modified Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[17] were assessed. The presence of infection, anemia, acute metabolic acidosis, dysnatremia, and therapeutic details such as mechanical ventilation and sedation medication were noted. Anemia was diagnosed if the patient's blood test during ICU admission showed hematocrit less than 30%. Acute metabolic acidosis was documented if there was a result of arterial blood gas analysis, performed during ICU admission showed blood pH less than 7.25 with partial carbondioxide pressure lower than 40 mmHg. Dysnatremia was defined as having serum sodium lower than 135 mmol/l or more than 145 mmol/l during ICU admission. Clinical-outcomes data such as the hospital length of stay and the hospital mortality rate were explored between the delirium and non-delirium groups.

Statistical analysis

All data analyses were performed using SPSS Statistics version 18 (SPSS, Inc., Chicago, IL, USA). Continuous data were checked for normal distribution by using Shapiro-Wilk test. All continuous data with normal distribution were presented using mean and standard deviation. The continuous variables with non-normal distribution were presented with median and interquartile range. To comparison between delirium and non-delirium group, the independent *t*-test was used to compare the continuous variables with normal distribution, and Mann-Whitney U test was used for non-normal data distributions. Categorical data are presented in percentages indicating the prevalence of the factor in either the delirium or the non-delirium group. Pearson Chi-squared or Fisher exact test was used, when suitable, to compare the categorical data between groups. Univariate analysis was performed to identified independent predictive factors associated with delirium during ICU admission. All the variables with a P-value less than 0.1 in univariate analysis were included in multivariate analysis. The logistic regression multivariate analyses were used to calculate the differences between the delirium and non-delirium groups. In the multivariate model, P-values less than 0.05 were considered statistically significant.

Ethical statement

The study protocol was reviewed and approved by the Institutional Review Board of Siriraj Hospital, Mahidol University (Si 707/2013).

RESULTS

A total of 88 patients underwent initial screening. Of these, 74 fulfilled the entry criteria and were enrolled in the study. Among 14 patients who were excluded, nine had RASS <-3 (n=9); two had a diagnosis of psychosis; and three were under sedative medications. By using the Thai version of CAM-ICU, a diagnosis of delirium was made for 28 patients (38%). Table 1 presents the general information regarding the patients who developed delirium and those who did not. Patients with delirium were older (67.8±15.7 vs. 53.6±19.2 year, p = 0.002). However, patients' basic ADL, ICQCODE, and APACHE II scores were similar. There was no difference among underlying diseases, except that more dementia patients were found in the delirium group [4 out of 28 patients (14.3%) vs. 1 in 46 patients (2.2%), p = 0.04]. The reasons for ICU admission included sepsis/septic shock (35 patients, 47.2%), respiratory failure (27 patients, 36.5%), acute myocardial infarction (five patients, 6.7%), and hemorrhagic shock (three patients, 4%). Also, there was no difference in the causes of admission among the groups. The sedative and analgesic medications were used in small proportion of our patients, which was no significant different between groups. (Table 2)

Physiologic alteration and the treatment and outcomes of patients with and without delirium are shown in Table 2. There was a higher proportion of anemia and acute metabolic acidosis in the delirium group [anemia 26 (92.9%) vs. 31 (67.4%), p = 0.01 and acute metabolic acidosis 20 (71.4%) vs. 16 (34.8%), p = 0.002]. As for ICU treatment, a higher proportion of delirium patients underwent mechanical ventilation [26 (92.9%) vs. 34 (73.9%), p = 0.04], while the use of vasopressors and renal-replacement therapy were similar. Eleven patients in this study died and 10 had delirium. Thus, hospital mortality was much higher in the delirium group [10 (35.7%) vs. 1 (2.2%) patients, p <0.001]. The duration of admission tended to be longer in the delirium group, but did not reach a significant limit [28.1+17.7 vs. 21.2+13.5 days, p = 0.06].

Factors associated with delirium were examined, as is shown in Table 3. Univariate analysis revealed that dementia, anemia, acute metabolic acidosis, and mechanical ventilatory support were associated with the occurrence of delirium. After being adjusted in multivariate analysis, we found that, for age > 70 years, anemia and acute metabolic acidosis remained significant, with odd ratios of 3.53 (1.01-12.36), p = 0.04; 8.24 (1.16-58.35), p = 0.04; and 5.90 (1.71-20.37), p = 0.005, respectively.

DISCUSSION

In sum, using the Thai version of CAM-ICU, we found that a substantial proportion of our medical ICU patients had delirium. This condition was significantly associated with age > 70 years, anemia, and acidosis. Delirium resulted in higher mortality and tended to prolong one's hospital stay.

The prevalence of delirium in our study paralleled what others have concluded. First, the "Delirium Epidemiology in Critical Care (DECCA)" study, a one-day point-prevalence study in 104 intensive care units across Latin America, along with two centers in Spain and the U.S.,[20] produced interesting results. The majority of patients had a medical condition. By using the CAM-ICU, those researchers identified delirium in 32% of the patients. They also noted a threefold increase in ICU mortality and a greater-than-twofold increase in the median ICU length of stay among delirium patients. Further, Ely et al., reported a high delirium prevalence in medical ICUs. With reference to the DSM-IV criteria, 39 (81.3%) of 48 patients developed delirium, and of these, 29 (60.4%) had delirium while still in the ICU. The researchers also found that the condition was strongly associated with prolonged hospital stays. Recently, a report from India[21] was based on 280 medical ICU patients. By using the CAM-ICU, researchers identified a delirium prevalence of 31.4%. Of these, approximately 56% had the hypoactive type, while 34% and 10% were of the hyperactive and mixed type, respectively. Like others, patients with delirium had a longer hospital stay and a higher one-month post-discharge mortality. Report from the surgical ICU of our institution[22] revealed a delirium incidence of 24%. Age, diabetes mellitus, severity of disease, postoperative use of benzodiazepines and mechanical ventilation were independent risk factors. Our results here reveal the same prevalence. Interestingly, approximately one- third (35.7%) of delirium patients died, and almost all (90.9%) of the patients who died had delirium.

Although the pathophysiology of delirium is not completely understood, evidence suggests that imbalanced neurotransmitter activity such as decreased acetylcholine, increased dopaminergic activity, and a deranged serotonin level play important roles. Impaired oxidative metabolism such as shock, sepsis, and decreased cerebral perfusion are common leading factors. This is a prevailing explanation for the significant association of anemia and acute metabolic acidosis in this report. These conditions, together with advanced age (>70 years), were comparable to what other studies have shown. However, other risks identified only in univariate analysis in our study were significant

TABLE 1. Patients' baseline characters.

Clinical Characters	Delirium *(n=28)*	Non-Delirium *(n=46)*	*P*
Age, years	67.8+15.7	53.6+19.2	0.002
Age >70 years, n (%)	14 (50.0)	13 (28.3)	0.06
Male gender, n (%)	17 (60.7)	22 (47.8)	0.28
APACHE II score†	19.2+8.0	16.5+7.3	0.14
APACHE II score >20	14 (50.0)	13 (28.3)	0.06
Underlying conditions, n (%)			
Diabetes mellitus	10 (35.7)	12 (26.1)	0.38
Hypertension	9 (32.1)	13 (28.3)	0.72
Chronic kidney disease	9 (32.1)	7 (15.2)	0.09
Chronic ischemic heart disease	4 (14.3)	6 (13.0)	0.88
Chronic lung disease	3 (10.7)	6 (13.0)	0.77
Atrial fibrillation	3 (10.7)	5 (10.9)	0.98
Cerebrovascular disease	4 (14.3)	3 (6.5)	0.27
Cirrhosis	2 (7.1)	4 (8.7)	0.81
Dementia	4 (14.3)	1 (2.2)	0.04
Reasons for ICU admission, n (%)			
Septic shock	15 (53.6)	20 (43.5)	0.4
Acute respiratory failure	10 (35.7)	17 (37.0)	0.91
Acute myocardial infarction	2 (7.1)	3 (6.5)	0.66
Hemorrhagic shock	2 (7.1)	1 (2.2)	0.29

Data are presented as mean+standard deviation or number (percentage per group)
†The APACHE II (Acute Physiology and Chronic Health Evaluation) score, a severity-determining score, ranges from 0 to 71. Higher scores indicate a more severe disease.

TABLE 2. Patients' clinical events, treatments, and outcomes.

Clinical characters	Delirium *(n=28)*	Non-Delirium *(n=46)*	P
Acute physiologic conditions, n (%)			
Anemia	26 (92.9)	31 (67.4)	0.01
Dysnatremia	23 (82.1)	28 (60.9)	0.06
Acute metabolic acidosis	20 (28.6)	16 (34.8)	0.002
Sedative and analgesic agents, n (%)			
Benzodiazepine plus opioid analgesia	3 (10.7)	9 (19.6)	0.36
Opioid analgesia alone	2 (7.1)	8 (17.4)	0.30
Benzodiazepine alone	2 (7.1)	6 (13.0)	0.48
Treatment during ICU admission, n (%)			
Mechanical ventilation	26 (92.9)	34 (73.9)	0.04
Receiving vasopressors	19 (67.9)	24 (52.2)	0.19
Require renal- replacement therapy	4 (14.3)	5 (10.9)	0.66
Duration of admission†, days	28.1+17.7	21.2+13.5	0.06
Duration of admission >30 days, n (%)	11 (39.3)	10 (21.7)	0.10
Hospital mortality, n (%)	10 (35.7)	1 (2.2)	<0.001
RR 7.86 (95%CI: 1.21-51.25)			

† Duration of admission was overall hospital admission day

TABLE 3. Predictive factors associated with new-onset delirium during ICU admission.

Clinical characters	Univariate analysis			Multivariate analysis		
	Relative risk	95% CI	P	Relative risk	95% CI	P
Age >70 years	1.46	0.95-2.25	0.06	3.53	1.01-12.36	0.04
Chronic kidney disease	1.54	0.86-2.76	0.09	2.39	0.58-9.82	0.23
Dementia	2.30	1.33-3.97	0.04	3.86	0.31-48.01	0.99
APACHE II score >20	1.46	0.95-2.25	0.06	3.04	0.93-9.97	0.07
Anemia	3.88	1.02-14.69	0.01	8.24	1.16-58.35	0.04
Abnormal electrolyte	2.08	0.90-4.77	0.06	1.14	0.25-5.27	0.29
Acute metabolic acidosis	2.64	1.34-5.22	0.002	5.90	1.71-20.37	0.005
Mechanical ventilation	3.03	0.81-11.30	0.04	4.64	0.67-32.05	0.12

in others.[21] Moreover, we did not find any link between delirium and the uses of certain medications, such as anticholinergics, benzodiazepines, and opiates, which was significant in the surgical ICU.[22] The low number of patients and the infrequent use of sedation in our unit are possible explanatory factors.

Knowing the mortality risk of delirium and its associated factors, we can take measures to prevent this condition. Rapid restoration of shock will mitigate the perfusion deficit, acidosis, and inflammation.[23-25] Timely source control of sepsis can lead to successful resuscitation. Thoughtful uses of organ support, namely mechanical ventilation and renal-replacement therapy, can minimize physiologic derangement stemming from life-saving measures.

Apart from the above findings, our study and earlier works support the use of the CAM - ICU as a bedside diagnostic tool for delirium. The simplicity and repeatability of the test enable clinicians to perform it routinely. Intensivists can conduct the test during daily rounds. Early recognition of acute brain dysfunction enables early intervention.

Our study had some limitations. First, the number of patients was small, as compared to other studies. The relatively small sample sized could resulted in inadequate power to detect the actual predictive factor, as well as, the wide range of 95% confidence interval for each predictive factor. A larger number might allow us to identify more predictive factors associated with delirium. Moreover, the study period was short, both in terms of the recruitment period and the duration of the follow-up. A longer study period should enable us to recruit more patients and detect both physical and cognitive impairments which have been found in other studies.[26,27] Finally, this study enrolled patients during August to December 2013. The progression of medical technology and treatment strategy now a day might affect to the nature of delirium among critically ill patients. Physician who decide to apply the results of this study to their clinical practice should carefully evaluate the context of this study and compare it with their own situation.

In conclusion, our report demonstrates that, by using the Thai version of the CAM-ICU, it was determined that approximately one-third of medical ICU patients had delirium. Patients with this condition had a high mortality and a prolonged hospital stay. In addition, some factors associated with this condition were identified. Aggressive resuscitation of critically ill patients in order to avoid these risks, such as early goal-directed resuscitation and optimum metabolic support, are essential to success.

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Correlation of Thyroid Hormones in the Prognosis of Critically Ill Patients

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ABSTRACT

Objective: Non-thyroidal illness syndrome (NTIS) is associated with outcomes in Intensive Care Unit (ICU) patients. The objectives of the study were to assess the prognostic value of complete thyroid profile in critically ill patients and to determine the effect of thyroid hormone level in predicting mortality when used along with acute physiology and chronic health evaluation (APACHE) II score.

Methods: The observational study was conducted at a tertiary care centre in Kolhapur, India. Critically ill adult patients admitted to intensive care units with APACHE II >10 was included (n=50). Relevant clinical investigations along with thyroid profile evaluation was carried out and APACHE II was calculated. Baseline characteristics of patients were compared. Performance of variables in predicting mortality was analysed. Correlation of APACHE II score with thyroid was also assessed in R software v-3.6.1.

Results: The survival rate at ICU discharge was 54%. Mean T3, FT3, and T4 levels were significantly low in non-survivors (p=0.006758, p=0.0245 and p=0.00070 respectively). Mean APACHE II score was significantly high in non- survivor (p=2.94E-^{06}). APACHE II score was significantly associated with the severity of disease (p=0.0235). APACHE II scores and FT3 were better predictors of mortality compared to other thyroid hormones (AUC =0.8519 ± 0.0535). FT3 showed high correlation with APACHE II score (r=-0.4083; p=0.0032). Inclusion of thyroid hormone levels with APACHE II scores improved the prediction of mortality in critically ill patients by 5.63%.

Conclusion: Among thyroid hormones, FT3 is a better predictor of mortality. Use of thyroid hormone levels in conjunction with APACHE II scores improves the prognostication.

Keywords: APACHE; euthyroid sick syndrome; thyroid (Siriraj Med J 2021; 73: 161-166)

INTRODUCTION

During critical illness, alteration in hormone levels is a commonly noted phenomenon.[1] The severity of the illness and the outcomes of the patients in Intensive care units (ICU) are associated with these alterations.[2,3] Thyroid hormones regulate the body's metabolism and immunity and thereby plays a vital role in maintaining body homeostasis.[4] Alterations in the thyroid hormone levels are characterized by relatively low levels of triiodothyronine (T3), high levels of reverse T3 (rT3) along with normal or low levels of thyroid-stimulating hormone (TSH) and thyroxine (T4); this alteration in thyroid hormone level is known as 'euthyroid sick syndrome or non-thyroidal illness syndrome' (NTIS).[5,6] Previous studies have reported the association between NTIS and outcomes in critically ill patients with various disorders such as multiple trauma, sepsis, respiratory failure, acute respiratory distress syndrome, mechanical ventilation and also in a few unselected critically ill patients.[7-12]

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Although, there are many prognostic models that considers biochemical and clinical parameters, their accuracy is low and hence not reliable.[13] The Acute physiology and chronic health evaluation (APACHE) II score with 77% accuracy is the most common method used to predict outcomes of patients in ICUs.[13] However, APACHE II scores do not consider hormonal responses, especially the levels of thyroid and cortisol hormones, which show association with outcomes in critically ill patients.[14]

Therefore, the study was designed to evaluate the usefulness of thyroid hormone levels in predicting mortality and also to ascertain if the inclusion of thyroid hormone levels at admission to ICU along with APACHE II improves mortality prediction in critically ill patients.

MATERIALS AND METHODS

The observational study was conducted at a tertiary care centre in Kolhapur, India. The study was approved by the Institutional Ethics and Research Committee (DYPU/2013/493). Written informed consent was obtained. The minimum sample size was calculated (n=~ 44) considering 80 % power with 95 % level of significance in R studio (v 1.2.5001) software using appropriate R code (pwr.t.test (effect size = 0.43, power = 0.80, significance level = 0.05, type =»one.sample»)). A total of 50 critically ill patients above the age of 18 years, admitted to the ICU with APACHE II scores > 10 were included in the study. Pregnant women, patients with a history of thyroid disease, patients on medications such as corticosteroids, dopamine, amiodarone, iodine & iodine containing contrast agents which alters the levels of thyroid hormones and those undergoing hormonal therapy for any reason were excluded.

Data regarding demographics and clinical history were recorded at the time of ICU admission. Thorough clinical examination was carried out. Total blood count, renal function, serum electrolytes, serum protein and arterial blood gas analysis were recorded, and APACHE II score was calculated for all the patients. Apart from other relevant examination, thyroid hormone analysis (T3, fT3, T4, fT4 and TSH) was done by Electro-chemiluminescence assay method on Roche Cobas e411. The normal reference ranges of thyroid hormone taken were T3 (1.2-2 nmol/L), fT3 (3.5-6.5pmol/L), T4 (70-150 nmol/L), ft4 (11.5-23 pmol/L) and TSH (0.3-4.5 µIU/L).[15]

Statistical analysis

The data collected was analysed in R software (version 3.6.1). Baseline characteristics of survivor and non-survivor patients at ICU discharge was compared by T test and Wilcoxon-Sign-Rank Test. Univariate logistic regression was used to obtain receiver operating characteristic (ROC) curve, from which AUC was calculated (cut-off value=0.5) to analyse the performance of variables in predicting mortality. Spearman Rank correlation test was used to assess the correlation of APACHE II score with thyroid profile.

RESULTS

The mean age of the participants was 53.68±14.70 years. The gender distribution was balanced with 62% male patients (n=31) and 38% female patients (n=19).

Rate of NTIS was 80% (n=40). Low Free T3 was observed in 52% cases (n=26). Whereas, low T3, T4, Free T4 and TSH were present in 40% (n=20), 44% (n=22), 38% (n=19) and 10% (n=5) of the cases, respectively. Of the 50 patients, 27 (54%) survived and were discharged from ICU.

Baseline characteristics of all the patients and the mean difference among the survivor and non-survivor patients is given in Table 1.

APACHE II score was significantly associated with the severity of disease and had the highest probability for predicting the mortality (p=0.0235; AUC=0.8519±0.0535) followed by FT3 (AUC=0.7536±0.0688) (Table 2). TSH was more likely to increase the chances of mortality (OR-0.75403; p=0.0235).

Significant negative correlation was observed between APACHE II score and T3 (r= -0.307; p=0.0302), FT3 (r= -0.4083; p=0.0032) and TSH (r=-0.2887; p=0.0419).

Significant positive correlation was observed between APACHE II score (r= 0.6106). Inclusion of thyroid hormone levels with APACHEE II scores, improves the prediction of mortality in critically ill patients by 5.63%. (Table 3, Fig 1)

DISCUSSION

Chronic critical illness is known to be linked with dysfunction of thyroid, adrenal gland and neuroendocrine axes resulting in decreased levels of various factors including thyroid hormones, insulin-like growth factor 1, sexual hormones, dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), prolactin and cortisol.[12] Therefore, this study was conducted to determine the use of thyroid hormones level along with APACHE II score for prediction of mortality in 50 critically ill patients. Majority of patients were above 40 years with a mean age of 53.68±14.70 years. Male predominance was noticed in the study (62%). Incidence of NTIS was 80%. Low levels of Free T3 in 52% of cases, T3 in 40% cases, T4 , Free T4 and TSH in 44%, 38% and 10% respectively were noticed

TABLE 1. Baseline characteristics.

Variables	All (n=50)	Survivor (n=27)	Non-survivor (n=23)	*p* - values
Mean age (years)	53.68 ± 14.70	52.04±15.22	55.61±14.16	0.3947
Male (%)	62	55	45	0.6115
Female (%)	38	53	47	1
Mean T3 [86-187 ng/dl]	89.98 ± 26.08	99.48±23.74	78.83 ± 24.67	0.006758*
Mean T4 [4.5-10.9 mcg/dl]	5.11 ± 2.13	5.72±2.15	4.39 ±1.91	0.0245*
Mean FT3 [3.10-6.80 pmol/L]	2.93 ± 1.06	3.38±1.01	2.41±0.87	0.00070*
Mean FT4 [11.4-22.1 pmol/L]	12.82 ± 3.93	13.44±3.25	12.10±4.57	0.2476
Mean TSH 0.35-5.5 mIU/L	0.86 ± 0.42	0.92±0.33	0.79±0.50	0.2936
Mean APACHE II score	24.38 ± 7.07	20.33±4.76	29.13±6.41	$2.94E^{-06*}$

*statistically significant; T3-Triiodothyronine; T4- Thyroxine; FT3- Free Triiodothyronine; FT4-Free Thyroxine; TSH- Thyroid stimulating hormone; APACHE- Acute Physiology And Chronic Health Evaluation

TABLE 2. Performance of variables in prediction of mortality using AUC.

Variable	AUC ROC	Sensitivity (%)	Specificity (%)
T3 [86-187 ng/dl]	0.7246 ± 0.0754	81.48	65.22
T4 [4.5-10.9 mcg/dl]	0.6844 ± 0.0790	74.07	65.22
FT3[3.10-6.80 pmol/L]	0.7536 ± 0.0688	74.07	65.22
FT4[11.4-22.1 pmol/L]	0.6457 ± 0.0856	85.19	52.17
TSH 0.35-5.5 mIU/L	0.6095 ± 0.0853	77.78	43.48
APACHE II score	0.8519 ± 0.0535	81.48	73.91

T3-Triiodothyronine; T4- Thyroxine; FT3- Free Triiodothyronine; FT4-Free Thyroxine;
TSH- Thyroid stimulating hormone; APACHE- Acute Physiology And Chronic Health Evaluation

TABLE 3. Inclusion of thyroid hormone level with APACHE II score in prediction of mortality.

Variables	AUC ROC	Percentage change in AUC (%)
APACHE II	0.8519	-
APACHE II + FREE T3	0.8712	1.93
APACHE II + FREE T4	0.8792	2.73
APACHE II + T3	0.88	2.81
APACHE II + T4	0.8824	3.05
APACHE II + T3 + T4 + free T3 + free T4 + TSH	0.9082	5.63

T3-Triiodothyronine; T4- Thyroxine; FT3- Free Triiodothyronine; FT4-Free Thyroxine;
TSH- Thyroid stimulating hormone; APACHE- Acute Physiology and Chronic Health Evaluation

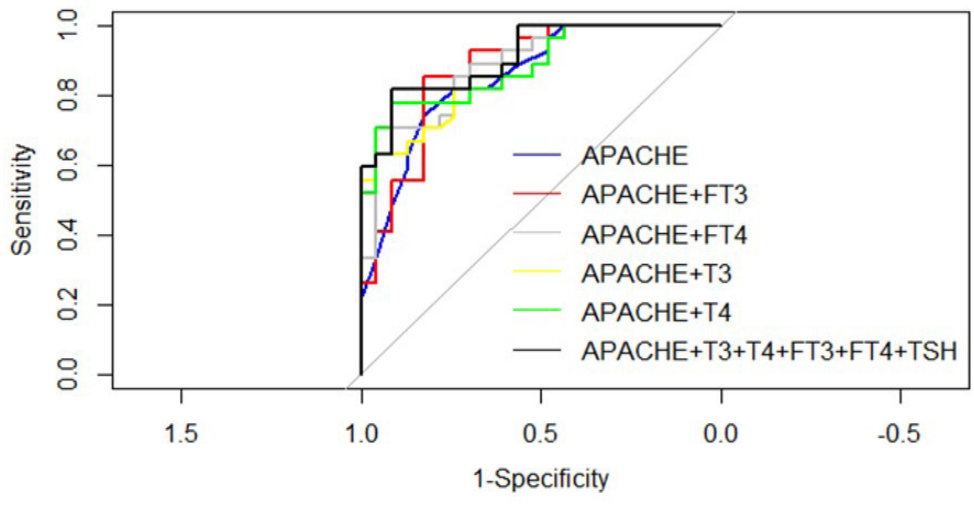

Fig 1. ROC curve showing the improvement in prediction of mortality with inclusion of thyroid level hormone.

and was probably due to the relationship between stress, illness and thyroid hormones.[15] Chronic stress leads to various illnesses ranging from mild to severe forms and also slows down the function of the thyroid gland.[15,16] Due to this, hormone production slows down resulting in fall in hormone level.[16] However, fall in the thyroid hormone level will have an effect on the functioning of the thyroid hormone including myocardial contractility, neural growth and differentiation, bone formation, regulation and resorption, metabolism, development and functioning of white and brown adipose tissue and cholesterol.[17] TSH level remains normal or slightly reduced and this is noticed in the study by low TSH in only 10% of the patients.[18] Of the cases, 56% of them survived at ICU discharge. Although, the high mean age of non-survivors depicted that there might be some correlation between age and outcome of the patients, there was no significant difference in age among both the groups (p=0.3947). This concurs with the study conducted by Gutch M et al. who also reported that there was no significant difference in age between the groups.[1] There was no significant difference in gender distribution among both the groups in this study (Male-p=0.6115; Female p=1).

Among non-survivors, the levels of T3, T4 and FT3 were significantly low (p<0.05). No significant difference was observed in FT4 levels between survivors and non-

survivors. Zargar AH et al., Hari Kumar K. V. S et al., Wang F et al. and Topla Y et al. have reported significant difference in levels of T3 and FT3 between survivor and non-survivors but not in T4 levels.[19-22] This can be attributed to the nature of illness. Interestingly, Faber J et al., has reported normal levels of FT3 and FT4 but has emphasized that reduction in T4 levels is proportional to severity of illness as well as length of illness.[23] This could be due to ultrafiltration technique which fails to exclude the thyroid hormone–binding proteins from the filtrate and gives spuriously high free hormone values.[24] No significant difference has been found in TSH level among both the groups (p=0.2936).[19-22] However, the varied assay methods may have contributed to the differences in the levels of thyroid hormone among the various studies.

APACHE II score is frequently used to predict mortality in patients with various kinds of illnesses.[25] Among the non-survivors, the APACHE II scores was significantly high indicating the severity of illness (p=2.94E-06). Khoshfetrat M et al. also reported significantly high APACHE II score among non- survivors.[26] APACHE II scores and FT3 had high probabilities in the prediction of mortality.[15] Comparatively, FT3 is highly correlated with APACHE II score (r= -0.4083; p=0.0032).[20] Hence is better suited for the prediction of mortality. Interestingly, Ray DC et al., Chinga-Alayo E et al. and Plikat et al. reported that T4, T3, FT4 and TSH are good predictors of mortality.[27-29] This difference in the findings can be attributed to the small sample size of these studies, no comparison with FT3 and population based differences.

The addition of all thyroid hormone levels to APACHE II score increases the rate of prediction by 5.63%. Plikat K et al. have also reported that considering baseline thyroid hormone levels can improve the predictive capacity of APACHE II.[29]

Usually, the dysfunction of thyroid in critically ill patients depends on the onset time of the illness. However, the study is limited as the onset time of the critical illness was not recorded. Also, the thyroid profile was assessed only during the admission to ICU. Moreover, hypothalamic pituitary axis parameters were also not considered in this study. However, considering the onset time, the more frequent assessment of the thyroid hormone profile and assessment of hypothalamic pituitary axis parameters would help in better prediction of mortality among the critically ill patients.

CONCLUSION

Among the thyroid hormones, FT3 is a better predictor of mortality. Combining thyroid hormone levels with APACHE II score improves the mortality prediction of critically ill patients and can be included as a part of the protocol in managing critically ill cases requiring intensive care.

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Factors Predicting Fatigue in Pulmonary Tuberculosis Patients Receiving Anti-Tuberculosis Drugs

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ABSTRACT

Objective: To explore the predictive factors on fatigue among pulmonary tuberculosis patients receiving anti-tuberculosis drugs.

Methods: This study is a predictive correlational research designed. The sample was comprised of 125 patients at the out-patient department, a tertiary hospital in Bangkok setting. The data were collected between January to February 2020. The questionnaires included mini-cognitive assessment instrument (Mini-Cog); the demographic characteristics questionnaire; Piper fatigue scale-12 (PFS-12); Nutrition alert form (NAF); the Pittsburgh sleep quality index (PSQI); and the Center for epidemiologic studies depression scale (CES-D). All data were analyzed by using descriptive statistics and multiple regression analysis.

Results: The sample had a mean age of 58.45 years (SD = 15.374) of which 60.8% were males. Overall, the mean score of fatigue was a moderate level (Mean = 4.90, SD = 2.455). From the multiple regression analysis, age, nutritional status, sleep quality, and depression could explain the variances on fatigue in the sample group as 52.5% (R^2 = .525, F = 33.119, $p < .001$). Nutritional status, sleep quality, and depression are the variables found to be capable in predicting fatigue of pulmonary tuberculosis patients with statistical significance ($\beta = .316$, $p < .001$, $\beta = .226$, $p < .05$ and $\beta = .340$, $p < .001$).

Conclusion: Nutritional status, sleep quality, and depression could affect fatigue. Healthcare teams should assess patients to prevent and manage the aforementioned symptoms to reduce suffering from fatigue and a better quality of life.

Keywords: Depression; fatigue; nutritional status; pulmonary tuberculosis patients; sleep quality (Siriraj Med J 2021; 73: 167-173)

INTRODUCTION

Due to consistently high incidence, Tuberculosis is a major public health problem of the past and present day. The primary causes of the spread of TB are the spread of HIV, poverty, migration and migrant labor movements. The World Health Organization expected the incidence of new patients and relapses for the world to be as high as 10.4 million baht, or 140 per hundred thousand people, or 1.7 million deaths per year.[1]

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Thailand is one of 14 countries with problems from high TB burdens. Incident reports found 108,000 new and relapsed patients, or 156 patients per hundred thousand people with 11,000 patients who had TB with HIV infections, 3,900 drug-resistant tuberculosis patients and 12,000 deaths per year. Tuberculosis is more predominant among males than females at a ratio of 1.91:1. In an ordinary tuberculosis patient case, the costs of drugs and pharmaceutical supplies amount to 2,600 baht, 200,000 baht in patients with drug-resistant tuberculosis and 1.2 million baht in patients with severe drug-resistant tuberculosis.[2] According to reports on tuberculosis patient statistics at a tertiary hospital in Bangkok setting for five years in retrospect, a tertiary hospital in Bangkok setting had 1,635 to 2,192 patients in 2014 to 2018.[3] Therefore, tuberculosis is a problem with international public health and economic significance.

Tuberculosis is a highly communicable respiratory disease. Medication adherence effectively treats and controls the transmission of tuberculosis in addition to relieving symptoms that cause patients discomfort until they recover. However, fatigue continues to be found.[4] In addition to being an effect of the pathology, fatigue can occur from side effects of many tuberculosis drugs.[5] Therefore, if patients have fatigue while receiving tuberculosis drugs, patients may become uncooperative in taking medications, causing multidrug-resistant tuberculosis, severe complications and higher treatment costs.[6] Therefore, the researcher's interest is in exploring the factors predicting fatigue in order to lead to assessment and planning of care to prevent factors affecting fatigue among patients with tuberculosis.

Research on the incidence of fatigue was found among many previous studies, (83%).[7] No studies on the predictors of fatigue among patients with pulmonary tuberculosis were found domestically or internationally. However, studies were found to have been conducted among patients with infections and other chronic illnesses. The conceptual framework of Piper et al.[8] was found to be an accepted theory on fatigue. In this study, however, the researcher selected four factors based on the aforementioned concept consisting of age, nutrition, sleep quality and depression.

MATERIALS AND METHODS

Ethical considerations

This study was considered and confirmed by the Institutional Review Board, Faculty of Medicine, a tertiary hospital in Bangkok setting (Si 783/2019). The researcher provided data by considering the participants' right protection in three areas consisting of potential risks, benefits, and maintaining data confidentiality. In addition, the researcher responded to inquiries until patients understood and consented to participate in the study along with signing the informed consent form.

Methodology

This cross-sectional study was based on a predictive correlational research design with a hypothesis stating age, nutrition, sleep quality and depression can co-predict fatigue among patients with pulmonary tuberculosis receiving anti-tuberculosis drugs. The sample was 125 patients diagnosed with pulmonary tuberculosis who came to follow-up on treatments at the Medical and Surgical examination unit, Out-patient building, a tertiary hospital in Bangkok setting, from January to February 2020. The sample was selected by purposive sampling of patients meeting the following inclusion criteria: ages more than or equal to 18 years, administration of anti-tuberculosis drugs for more than two weeks and ability to communicate in Thai. The following exclusion criteria was applied: cognitive deficiency, co-morbidities causing proneness to fatigue such as AIDS, heart failure, end-stage chronic renal failure, end-stage liver disease, cancer, stroke, chronic obstructive pulmonary disease, asthma, psychiatric disorders, obstructive sleep apnea, pregnant or breastfeeding women and patients with unstable physical symptoms and presenting symptoms.

Sample size was set by using the G*power program, Version 3.1.9.4. Predictive relationships were analyzed using multiple regression analysis. Power of test was 0.8. Reliability (α) was at 0.05 with an effect size of 0.1.[9] This study had four variables (k) and this study obtained 125 subjects for hypothesis testing.

Instruments

Data collection questionnaires in this study were divided into the following 6 parts:

1) The Mini-Cognitive Assessment Instrument (Mini-Cog) Thai version. The instrument contained three questions. In Question 1, the elderly were instructed to repeat and memorize three words. In Question 2, the elderly were instructed to draw a clock with the needle pointing at the time of 11:10 am. In Question 3, the elderly were instructed to speak the words in Question 1. Patients with a total score of three points and up met inclusion criteria for the sample.

2) The demographic data and illness background recording form for patients. Part 1 contained 17 questions on demographic data such as gender, age, marital status, level of education, religion, occupation, income, treatment entitlements, lodging characteristics,

environment, cohabitation with other family members, mask-wearing behavior, separation of items, smoking, alcohol consumption and tuberculosis symptoms. Part 2 contained 4 questions on illness background data such as duration of illness and time when patients began taking anti-tuberculosis drugs, type of patients with tuberculosis, chronic illnesses or co-morbidities, anti-tuberculosis drug formulas and other drugs.

3) The Piper Fatigue Scale-12 (PFS-12) Thai version. The scale was developed with 12 questions assessing fatigue with coverage of the following four aspects: 1) behavior and severity; 2) perception; 3) feelings of physical and psychological fatigue; and 4) intellect and emotions. The scale's interpretation of fatigue was divided into four levels. High fatigue was in a score range of 7.00 - 10.00. Moderate fatigue was in a score range of 4.00 - 6.99. Light fatigue was in a score range of 0.01 - 3.99. No fatigue was in a score range of 0.00.

4) The Nutrition Alert Form (NAF) Thai version. For monitoring malnutrition risks with 18 questions. Interpretation was divided into three levels. Scores of 0 - 5 points meant no risk of malnutrition, scores of 6 - 10 points meant risk of malnutrition and scores of more than or equal to 11 points meant malnutrition.

5) The Pittsburgh Sleep Quality Index (PSQI) Thai version. The form contains 9 questions with 7 components on subjective sleep quality, time before sleep, sleeping hours, sleep efficiency, sleep disruption, use of sleep medication and effects on daytime activities. Scores were interpreted in the range of 0 - 21 points. Scores of more than five points meant poor sleep quality.

6) The Center for Epidemiologic Studies Depression Scale (CES-D) Thai version. The scale contains 20 questions for assessing depression in the past week. The scale had a score range of 0 - 60 points. Scores of more than 15 points meant depression.

Instrument quality testing

Research instruments were standard instruments. Content validity was tested by qualified experts and instruments were translated into Thai by the back-translation method. In addition, instruments were used to assess many subjects. The researcher with 30 patients who had the same qualifications as the sample and data were used to calculate reliability. Cronbach's Alpha Coefficient of the PFS-12 form was 0.946, 0.803 for the PSQI form and 0.872 for the CES-D form. The NAF had an inter-rater reliability score of 1.000 when used with 10 subjects. In a sample group with 125 subjects, the PFS-12 form had a reliability score of 0.963, 0.822 for PSQI and 0.888 for CES-D.

Data collection methods

The researcher collected data in person by using a letter to request permission to meet with the Head of out-patient nursing and asking for cooperation from nurses at the Medical and Surgical examination unit to survey the names of patients with tuberculosis who met inclusion criteria and bring the researcher to meet with the sample group. The researcher introduced herself, explained research objectives, data collection procedures, protection of the rights of the sample group and asked for permission to use data from patient medical records. The researcher had the participants complete questionnaires by using 25 minutes per patient. After obtaining 125 subjects, the researcher ended data collection and analyzed data.

Statistical analysis

Data were analyzed and processed. The SPSS computer program was used to analyze demographic data and illness background. Descriptive statistics such as frequency distribution, percentage, mean and standard deviation were used to analyze predictive power of age, nutrition, sleep quality and depression. Fatigue among patients with pulmonary tuberculosis was analyzed using all enter multiple regression analysis.

RESULTS

Demographics, illness and treatment data

The sample was predominantly male (60.8%) with a male-to-female ratio of 1.55:1. The sample was aged 19-89 years at a mean of 58.45 years (SD = 15.374). Most of the sample was elderly (52.8%), married (60.8%), had highest level of education at the elementary level (40.8%) and Buddhist (96.8%). The sample was unemployed (42.4%), followed by the sample working as hired workers (17.6%) with income less than 5,000 baht (48.8%). The sample used universal health guarantee rights (40.8%) and lived in single homes (55.2%) with clean and clear environments (93.6%). During treatment, the sample was non-smoker (93.6%) and non-alcoholic (88.8%). Of the sample, 96.8% of the sample was new pulmonary tuberculosis patients with co-morbidities (48.8%). The top three co-morbidities encountered were hypertension (34.4%), diabetes mellitus (24%) and hyperlipidemia (23.2%). The sample (88%) had fatigue, received anti-tuberculosis drugs for one month (37.6%) and received the 2HRZE/4HR anti-tuberculosis drug formula (91.2%) with Vitamin B6 (96%).

Nutritional status

Mean nutrition scores were at the level of normal

nutrition (55.2%) (Mean = 5.38, SD = 4.065), followed by risk of malnutrition (36%) and malnutrition (8.8%).

Sleep quality

Mean sleep quality scores showed the participants to have poor sleep quality (65.6%) (Mean = 8.00, SD = 4.117) and some of the participants had good sleep quality (34.4%).

Depression

Mean depression scores showed the participants to have no depression (64.8%) (Mean = 13.70, SD = 9.813) and some of the participants had depression (35.2%).

Fatigue

Mean fatigue scores were at a medium level (52%) (Mean = 4.90, SD = 2.455), followed by high fatigue (18.4%). Concerning man fatigue scores in all four components, behavior and severity (Mean = 4.86, SD = 2.701), perception (Mean = 5.50, SD = 2.978) and physiological and psychological feelings (Mean = 5.69, SD = 2.997) were at a medium level while intelligence and emotions (Mean = 3.43, SD = 2.995) were at a low level (Table 1).

Correlation analysis

Correlation analysis using Pearson's Correlation Coefficient found age to not be correlated with fatigue among patients ($r = .034$, $p > .05$). Nutrition was positively correlated with fatigue with statistical significance ($r = .571$, $p < .01$), sleep quality was positively correlated with fatigue with statistical significance ($r = .580$, $p < .01$) and depression was positively correlated with fatigue with statistical significance ($r = .631$, $p < .01$) (Table 2).

Multiple regression analysis

All enter multiple regression equation analysis found all independent variables to be able to explain fatigue fluctuations in patients with pulmonary tuberculosis at 52.5% with statistical significance at .001 ($R^2 = .525$, $F = 33.119$, $p < .001$). Nutrition, sleep quality and depression were able to explain fatigue among patients with statistical significance ($\beta = .316$, $p < .001$, $\beta = .226$, $p < .05$ and $\beta = .340$, $p < .001$, respectively (Table 3).

TABLE 1. Piper Fatigue Scale-12 scores (n = 125).

Fatigue Level	Possible Range	Acquired Range	Amount	Percent
No Fatigue	0.00	0.00	15	12.0
Mild	0.01 - 3.99	1.50 - 3.92	22	17.6
Moderate	4.00 - 6.99	4.08 - 6.92	65	52.0
Severe	7.00 - 10.00	7.00 - 9.58	23	18.4

(Min = 0.00, Max = 9.58, Mean = 4.90, SD = 2.455)

TABLE 2. Results from analysis of correlation coefficients between age, nutritional status, sleep quality, depression and fatigue.

Variables	1	2	3	4	5
Age	1				
Nutrition	.141	1			
Sleep quality	.073	.445**	1		
Depression	.028	.469**	.635**	1	
Fatigue	.034	.571**	.580**	.631**	1

**Statistical significance at .01.

TABLE 3. Results from multiple regression analysis of age, nutritional status, sleep quality, depression and fatigue.

Variables	b	Std. Error	Beta	t	Sig
Constant	1.969	.661		2.977	.004
Age	-.006	.010	-.037	-.575	.566
Nutrition	.191	.044	.316	4.296	.000
Sleep quality	.135	.050	.226	2.707	.008
Depression	.085	.021	.340	4.007	.000

SE_{est} = ±1.72, R = .724, R^2 = .525, Adj. R^2 = .509, df = 4, 120, F = 33.119, Sig F = .000

DISCUSSION

This study found fatigue incidence at 88% with fatigue scores being at a medium level (52%). Fatigue can be explained as the most frequently encountered symptom among patients because the body needs energy from the oxygen metabolism process and reduced pulmonary functions from chronic inflammation due to the body's immune response to tuberculosis caused fatigue. In addition, loss of appetite was another nutritional problem resulting from cytokines related to inflammation, particularly TNF-alpha, causing patients to receive less energy and resulting in fatigue.[10] Furthermore, side-effects from anti-tuberculosis drugs also caused fatigue.[5]

Age was unable to predict fatigue among patients with pulmonary tuberculosis. This was inconsistent with the hypothesis and inconsistent with the conceptual framework on fatigue of Piper et al, which stated older persons can easily have fatigue due to reduced performance efficiency of various organs.[8] This study was consistent with previous studies conducted in similar population groups which found age to be unrelated to fatigue.[11] This was in conflict with this study, which found age to be related to fatigue.[12] Furthermore, age was not a factor with influence on fatigue.

Nutritional status was able to co-predict fatigue among patients with pulmonary tuberculosis with statistical significance ($\beta = .316$, $p < .001$). This was consistent with the hypothesis and conceptual framework on fatigue of Piper et al. who stated that, when the body receives insufficient nutrients, the body's internal mechanisms will use accumulated energy and muscles will release glycogen, protein and fat to use as energy, causing the body to be fatigued.[8] In the present study, the participants had poor nutrition, possibly due to weight loss (45.6%) from loss of appetite caused by cytokines related to inflammation, particularly TNF-alpha and Peptide YY.[5] Furthermore, the side-effects of anti-tuberculosis drugs were found to have effects on nutrition, thereby causing patients to lose appetite, feel nausea and vomit. Anti-tuberculosis drugs with side-effects consist of Isoniazid,[13] Rifampicin,[13] Pyrazinamide.[14] In particular, in the first two months during the intense stage, the participants were found to have significant energy use for metabolism, resulting in poor nutrition with more fatigue than the continuing stage. The findings from this study concurred with those of a previous study finding nutrition to be able to predict fatigue[15] and was in conflict with the findings from this study, which revealed nutrition to be uncorrelated with fatigue.[12]

Sleep quality was able to co-predict fatigue among patients with pulmonary tuberculosis with statistical significance ($\beta = .226$, $p < .05$). This was consistent with the hypothesis and the conceptual framework on fatigue of Piper et al., which stated that insufficient sleep, the body will be unable to produce high energy substances, accumulate protein or secrete hormones for growth, causing fatigue.[8] This can be explained physiologically that sufficient sleep was important for the body in storing and accumulating energy for use, causing individuals to feel fresh.[16] In this study, the participants were found to have poor sleep quality, possibly due to chronic coughing (31.2%).[17] In addition, the patients had night sweats (12.8%), which may be related to cortisol levels that suppress IL-1 functions. As a result, the patients had low fevers in the afternoon due to low cortisol and increases in TNF-alpha and IL-1, which were indicated to be cytokines secreted from cells in response to tuberculosis and to produce granuloma.[10] In addition, the side-effects

of anti-tuberculosis drugs such as Isoniazid, Rifampicin and Ethambutol were found to have effects on sleep quality.[18] This study was consistent with previous findings from studies revealing sleep quality to be correlated with and able to predict fatigue.[12,19] This conflicted with the findings revealing sleep quality to be unrelated to fatigue.[20]

Depression was able to predict fatigue among patients with pulmonary tuberculosis with statistical significance ($\beta = .340$, $p < .001$). This was consistent with the hypothesis and the conceptual framework on fatigue of Piper et al., which stated that psychological abnormalities are a cause of fatigue.[8] This can be explained in that the body triggers a response by synthesizing corticotrophin-releasing hormones when patients have depression, resulting in changes in the immune system with cytokines and TNF-alpha being detected. These substances cause effects cortisol and catecholamine secretion, resulting in tachycardia and increased metabolism. At the same time, insulin secretion will be suppressed. If the body accumulates stress over a long time, the body will use energy reserves, causing fatigue.[21] The participants were depressed, possibly due to thought they should isolate themselves in addition to feeling fear, hopelessness and stigmatization.[22] Furthermore, most of the participants were found to be income under 5,000 baht (48.8%), thereby causing patients to have insufficient income with effects on depression. This was consistent with the findings of a study which studied patients with low monthly income to be four times more likely to have depression,[23] ultimately resulting in fatigue. Anti-tuberculosis drugs with effects on depression consisted of Isoniazid.[13] This study was consistent with previous findings from studies revealing depression to be correlated and able to predict fatigue[19] which conflicted with the study which found depression to be uncorrelated with depression.[24]

Recommendations and implications

1. Healthcare team members should assess fatigue, nutrition, sleep quality and depression in every patients with pulmonary tuberculosis, particularly in the first two months of receiving anti-tuberculosis drugs in order to learn about problems while patients are being treated.

2. Nurse managers should be assigned to individual patients to provide knowledge and recommendations. In addition, programs for promoting nutrition and sleep quality should be prepared along with finding depression prevention guidelines for patients with pulmonary tuberculosis.

3. According to the findings, nutrition, sleep quality and depression were able to predict fatigue among patients with pulmonary tuberculosis at 52.5%, indicating other factors were related to fatigue. These factors may be used to study and explain fatigue phenomena more clearly.

4. An experimental research model for reducing fatigue should be developed such as nutrition programs and sleep quality promotion programs, etc., in order to provide guidelines to care for and support patients with pulmonary tuberculosis to be able to manage fatigue and have better quality of life.

CONCLUSION

Nutrition, sleep quality and depression had effects on fatigue in patients with pulmonary tuberculosis. Fatigue is a manageable factor. Healthcare teams should recognize the importance of consistent assessment, care and promotion of nutrition, sleep quality and depression to prevent and reduce suffering from fatigue, leading to recovery from pulmonary tuberculosis and better quality of life.

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Diagnosis and Initial Management of Agitated Patients in a General Hospital in Thailand

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ABSTRACT

Objective: This study aimed to examine the characteristics, diagnosis and management of agitated inpatients before psychiatric consultation in a general hospital and to explore the concordance between the diagnoses by attending physicians with that of consultant psychiatrists.

Methods: Medical records of inpatients aged 18 years or older that were referred for psychiatric consultation due to agitation in a general hospital in Thailand in 2018 were abstracted by a consultant psychiatrist. Data included (1) demographic and clinical factors, (2) the working diagnoses before the consultation, and final diagnoses by consultant psychiatrists, and (3) initial management.

Results: Of the 188 patients, confusion was the most commonly detected early sign of agitation (33.5%), while fidgeting was the most common symptom/behavior that led to psychiatric consultations (50.0%). The average onset time of agitation after admission was 62 hours 48 minutes. The most common cause of agitation was delirium due to a medical condition (47.3%). Primary psychiatric disorders were only found in 9 (4.8%) of agitated patients. There was a low diagnostic concordance between attending physicians and psychiatrists (Cohen's Kappa=0.32). Physical restraints were used in 109 (58.0%) patients, whereas 166 (88.3%) were prescribed with sedatives. Attending physicians prescribed benzodiazepine to ameliorate agitation in 32 (36.0%) of patients with delirium. However, 4 (7.3%) patients with alcohol-withdrawal delirium were untreated initially with benzodiazepine.

Conclusion: Medical conditions are more common causes of agitation than psychiatric illness. There is poor diagnostic concordance between attending physicians and psychiatrists, and high rates of physical restraints and benzodiazepine injection were found.

Keywords: Psychomotor agitation; delirium; alcohol withdrawal delirium; diagnosis; physical restraint; benzodiazepines
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INTRODUCTION

Agitation, defined as an excessive motor activity associated with a feeling of inner tension[1], is one of the most common emergency conditions in general practice.[2] Agitation can result from both psychiatric and medical conditions, including metabolic disturbances, traumatic brain injury, severe infections, dementia, delirium, and drug exposure.[3] Severe agitation can contribute to worse treatment outcomes and can be harmful to patients and hospital staff.[4-5] Agitated patients risk complications from

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impulsive behavior such as falls and removal of catheters and tubes.[6] Additionally, agitated patients often pose a threat of physical injury to other patients or caregivers. Up to half of health care workers report experiencing violence from agitated patients in the prior year, with the highest prevalence among nurses.[7]

Although there have been many proposed guidelines for the management of the patients with agitation, treatment results are generally unsatisfactory and evidence of agitation management in specific groups of patients are still limited.[8] A lack of universally accepted definitions and the complex and varied presentation of agitated patients presents a significant challenge for diagnosis and management.[9] Different settings and countries face altogether different problems in the management of agitation management. A growing body of literature tends to focus on settings such as psychiatric wards, intensive care units (ICUs), or emergency departments[10-12], a specific diagnosis (e.g., delirium, schizophrenia) or certain age groups[13], rather than on all agitated cases in the inpatient ward in a general hospital. To improve the quality of care for patients with agitation, we need to consider the heterogeneous characteristics of patients in all inpatient wards, and the common pitfalls of initial treatments.

We studied agitated patients in all inpatient wards in a general hospital, and used the results to develop a clinical practice guideline and to design medical education for the management of agitation. This study aimed to describe agitated patient characteristics, and examine the concordance between the diagnoses and initial management by attending physicians (APs) with that of consultant psychiatrists.

MATERIALS AND METHODS

Participants

This retrospective chart review consisted of inpatients aged 18 years and older referred for psychiatric evaluation due to agitation from 1 January to 31 December 2018 at Buddhachinaraj Hospital in Phitsanulok, Thailand. Agitation was defined according to expert consensus from the 1st International Meeting on Agitation in 2018[9] that includes (1) inability to stay calm or still, (2) motor and verbal hyperactivity and hyperresponsiveness, (3) emotional tension and (4) difficulties in communication. The following keywords were used as search terms to identify patients with agitation; motor hyperactivity (agitation, restless, unable to stay still, chaotic behavior, thrashing, shaking, removal of medical tubes and devices, physically violent behavior, hitting, kicking, elopement), verbal hyperactivity (screaming, angry ranting) and emotional tension (fearful, anxious and nervous). Patients with previous consultations with psychiatrists or those that had insufficient data in their medical records were excluded.

Setting

Buddhachinaraj Hospital is a 1,000-bed general medical hospital in Thailand with 19,050 admissions in 2018 and also serves as a medical education center for Naresuan University. There is no psychiatric ward or seclusion rooms. In case of agitation, the AP provides initial management before notifying a consultant psychiatrist who is required to see the patient within 24 hours.

Data collection

Medical records were abstracted by the first author during 1 January and 30 June 2019. Data included (1) demographic and clinical factors (e.g., alcohol and illicit drug use, history of surgery), (2) the working diagnoses (WD) by APs before the consultation, and final diagnoses (FD) by consultant psychiatrists, and (3) initial management before psychiatric consultation

Statistical analysis

Patient identifying information was removed and descriptive statistics were analyzed using SPSS version 22. Cohen's Kappa was calculated to test the agreement between the WDs given by APs and the FDs by consultant psychiatrists.

Ethics Approval

The Buddhachinaraj Phitsanulok Hospital Institutional Review Board (IRB) approved the study (IRB No.024/2020). Individual patient consent was waived by the IRB because data were de-identified before statistical analysis in this retrospective chart-review study.

RESULTS

Nine-hundred and eighteen patients were referred for psychiatric consultation in 2018 and 270 (29.4%) were consulted due to agitation representing 1.4% of all admissions. Patients who received treatment from psychiatrists before the consultation (n=72) and patients with incomplete data (n=10) were excluded. Therefore, data from 188 patients were analyzed.

Patient characteristics

One-hundred and fifty (79.8%) patients were male. The median age was 52 years (range 18-89; SD 15 years). One-hundred and twenty-four patients reported using alcohol (66.0%), 72 (38.3%) reported using tobacco and one patient reported using amphetamine (0.5%). At the

time of psychiatric consultation, 83 (44.1%) patients were admitted to General Surgery, 55 (29.3%) to Internal Medicine, 33 (17.6%) to Orthopedic Surgery, 5 (2.7%) to Ophthalmology and Ear-Nose-Throat, and 1 (0.5%) to Obstetrics and Gynecology wards. In addition, 6 (3.2%) were in an observation ward and 5 (2.7%) were in ICUs.

The most common principal diagnosis was "Injury, poisoning and certain other consequences of external causes" (35.1%, n=66), 17 (25.8%) of which had intracranial injuries. Among patients with a principal diagnosis of "mental and behavioral disorders" (13.8%, n=26), 84.6% were alcohol-related. The average number of comorbidities was 2.7 diseases per person. Twenty-seven (14.4%) patients did not have any comorbid disorders. Details of principal diagnoses, comorbidities, and past medical history are shown in Table 1.

Characteristics and detection of agitation

The average time of onset of agitation occurred was 62 hours 48 minutes after admission. Early signs of agitation noted in the medical records included confusion (63; 33.5%), fidget (51; 27.1%), chaotic behavior (31; 16.5%), and other symptoms such as thrashing, screaming, restless, aggression, removal of indwelling tubes and catheters, and "climbing out of a bed".

Initial interventions before psychiatric consultations

Once the presence of agitation was detected, initial interventions included physical restraint (109; 58.0%), sedative medications (166; 88.3%), and verbal de-escalation (1; 0.5%) (Fig 1). The mean time from detection of agitation to psychiatric consultation was two days. The most common reason for psychiatric consultation included fidget (94; 50.0%), followed by chaotic behavior (58; 30.9%), screaming or angry rants (12; 6.4%), violent behaviors (5; 2.7%), and leaving the hospital against medical advice (1; 0.5%). Documented violent behaviors include "kicking a nurse", "striking a visiting family member", and "threatening to hit a staff member".

Diagnoses: Causes of agitation

Of the 188 agitated cases, the FDs made by consultant psychiatrists were delirium due to a medical condition (89; 47.3%), alcohol withdrawal delirium (AWD) (55; 29.3%), alcohol withdrawal (AW) (27; 14.4%), and other psychiatric disorders (9; 4.8%), including schizophrenia, adjustment disorder, brief psychotic disorder, bipolar disorder, major depressive disorder and dementia. Eight patients were not diagnosed with any psychiatric disorders.

Concordance of diagnoses

The overall diagnostic concordance Cohen's Kappa (κ) was 0.32 suggesting a low level of agreement between diagnoses made by APs and psychiatrists. Of the 89 delirium FD cases, only 47 (52.8%) had a WD of delirium, demonstrating weak diagnostic concondance (κ=0.51) (Table 2). Twenty (22.5%) of patients with a FD of delirium were misdiagnosed as having alcohol withdrawal syndrome: AW (13; 14.6%), and AWD (7; 7.9%). In addition, 5 (5.6%) were misdiagnosed with other psychiatric disorders. A low level of agreement was found in diagnostic concordance of AW (κ=0.42) and 'other psychiatric disorders' (κ=0.58). The lowest concordance rate (κ=0.30) was found in diagnosing AWD (13; 23.6%). Most patients with this FD were initially diagnosed with AW (61.8%) by physicians.

Initial pharmacological management of agitation

Benzodiazepines were most commonly used for the initial management of agitation (112; 67.5%), followed by antipsychotics (42; 25.3%) (Table 3). Regarding benzodiazepine use, intravenous diazepam (5-10 mg) and oral lorazepam (0.5-4 mg) were prescribed to 85 (51.2%) and 27 (16.3%) patients, respectively. APs prescribed benzodiazepines to ameliorate agitation in 18 (36.0%) of patients with a WD of delirium (n=50) before psychiatric consultation (Table 4). Regarding the FD of delirium (n=89), 32 (36.0%) patients was prescribed with benzodiazepine. However, benzodiazepine was prescribed to only 51 (92.7%) patients with a FD of AWD; this left 4 (7.3%) patients untreated initially with benzodiazepine.

DISCUSSION

Agitation with variable presentation and initial management is a common problem. This study explored agitation in all wards of a general hospital, and was not limited to specific settings or populations, reflecting a real-world situation of agitation management in limited-resource settings. The strength of this study is that all patients were assessed and diagnosed by consultant psychiatrists to avoid limitation of previous studies where agitated patients were assessed by medical or psychiatry residents, and senior/trained nurses.[13,14]

We observed that most agitated cases referred for psychiatric consultation were caused by medical conditions and AWD. Only 4.8% of these referrals resulted from primary psychiatric disorders. Our findings offer useful insight for healthcare providers (HCPs) in the general hospital setting to be alert for medical conditions that

TABLE 1. Principal diagnoses, comorbidities and past medical history of patients referred for psychiatric consultation due to agitation (n=188).

Principal diagnosis (ICD-10)	N	%
Injury, poisoning and certain other consequences of external causes (S00-T98)	66	35.1
Diseases of the digestive system (K00-K93)	32	17.0
Mental and behavioral disorders (F00-F99)	26	13.8
Diseases of the circulatory system (I00-I99)	18	9.6
Diseases of the respiratory system (J00-J99)	10	5.3
Neoplasms (C00-D48)	8	4.3
Certain infectious and parasitic diseases (A00-B99)	6	3.2
Diseases of the musculoskeletal system and connective tissue (M00-M99)	6	3.2
Diseases of the nervous system (G00-G99)	5	2.7
Diseases of the genitourinary system (N00-N99)	4	2.1
Comorbidities (ICD-10)		
Endocrine, nutritional and metabolic diseases (E00-E90)	111	59.0
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	78	41.5
Diseases of the circulatory system (I00-I99)	58	30.9
Diseases of the respiratory system (J00-J99)	45	23.9
Injury, poisoning and certain other consequences of external causes (S00-T88)	42	22.3
Diseases of the digestive system (K00-K93)	39	20.7
Diseases of the genitourinary system (N00-N99)	36	19.1
Certain infectious and parasitic diseases (A00-B99)	25	13.3
Diseases of the musculoskeletal system and connective tissue (M00-M99)	23	12.2
Diseases of the nervous system (G00-G99)	13	6.9
Diseases of the skin and subcutaneous tissue (L00-L99)	11	5.9
Intracranial injury (S06)	9	4.8
Mental and behavioral disorders (F00-F99)	7	3.7
Neoplasms (C00-D48)	4	2.1
Past medical history		
Metabolic disease	**N**	
Essential hypertension (I10)	42	(22.3%)
Diabetes (E08-E13)	18	(9.6%)
Dyslipidemia (E78.5)	17	(9%)
Neurological disease		
Epilepsy (G40)	9	(4.8%)
Old cerebrovascular accident (CVA) (I63)	5	(2.7%)
Dementia (F03)	2	(1.1%)
Other neurological disorders (G98)	3	(1.6%)

TABLE 1. Principal diagnoses, comorbidities and past medical history of patients referred for psychiatric consultation due to agitation (n=188). (Continue)

Principal diagnosis (ICD-10)	N	%
Rheumatologic disease		
Gout (M10)	11	(5.9%)
Cardiovascular disease		
Atrial fibrillation (I48)	6	(3.2%)
Ischemic heart disease (I20-I25)	7	(3.7%)
Dilated cardiomyopathy (I42)	2	(1.1%)
Other cardiovascular diseases (I51.6)	6	(3.2%)
Renal disease		
Chronic kidney disease (N18)	8	
Psychiatric disorders		
Schizophrenia (F20)	4	(2.1%)
Alcohol-induced psychosis (F10.5)	1	
Alcohol use disorder (F10.1-F10.2)	1	
Bipolar disorder (F31)	1	
Major depressive disorder (F32-F33)	1	
Other diseases	37	(19.7%)

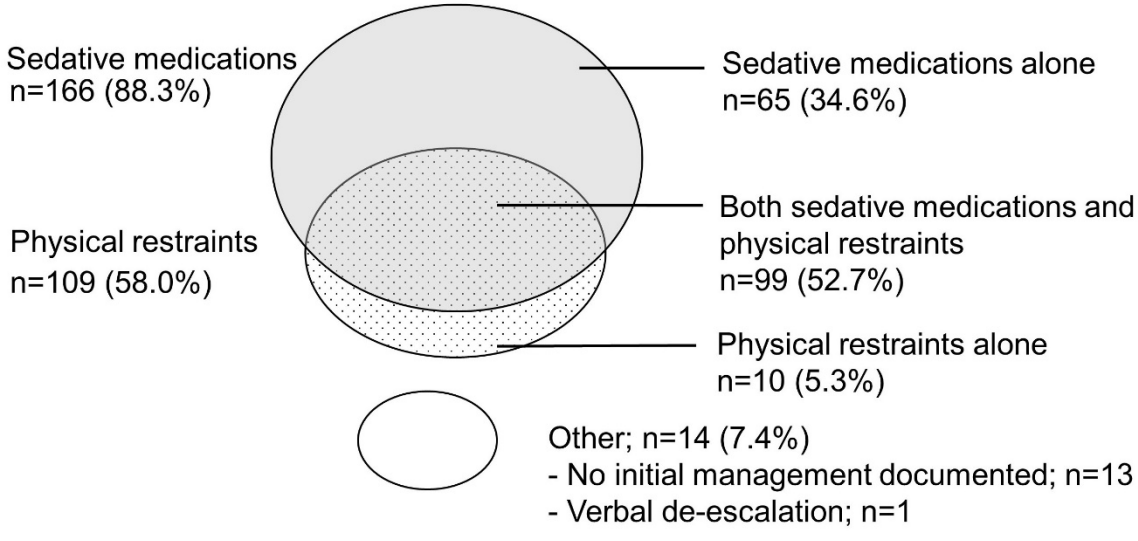

Fig1. Initial management of agitation before psychiatric consultation (n=188)

TABLE 2. Concordance between final diagnoses by psychiatrists and working diagnoses by physicians among inpatients with agitation.

Final diagnoses by psychiatrists	Working diagnoses by attending physicians	n	%	Cohen Kappa (κ)
Delirium due to a medical condition (n=89)	Delirium due to a medical condition	47	52.8	0.51
	Alcohol withdrawal	13	14.6	
	Alcohol withdrawal delirium	7	7.9	
	Psychiatric disorders	5	5.6	
Alcohol withdrawal delirium (n=55)	Alcohol withdrawal	34	61.8	
	Alcohol withdrawal delirium	13	23.6	0.30
	Delirium due to a medical condition	3	5.5	
	Psychiatric disorders	1	1.8	
Alcohol withdrawal (n=27)	Alcohol withdrawal	22	81.5	0.42
	Alcohol withdrawal delirium	1	3.7	
	Delirium due to a medical condition	-	-	
	Psychiatric disorders	-	-	
Other psychiatric disorders* (n=9)	Other psychiatric disorders	6	66.7	0.58

*Other psychiatric disorders include schizophrenia, adjustment disorder, brief psychotic disorder, bipolar disorder, major depressive disorder and dementia

TABLE 3. Initial medications prescribed by attending physicians to relieve agitation (n=166)

Medications prescribed before psychiatric consultation	Number of patients (%)	Mean dose (range) in mg	
		Parenteral injection	Oral
Benzodiazepine	112 (67.5)		
Diazepam	85 (51.2)	9.7 (5-10) (IV)	-
Lorazepam	27 (16.3)	- *	1.3 (0.5-4)
Antipsychotics	42 (25.3)		
Haloperidol	40 (24.1)	4.8 (2.5-5) (IM)	1.5 (0.5-2)
Quetiapine	2 (1.2)	-	18.8 (12.5-25)
Opioids	9 (5.4)		
Fentanyl	8 (4.8)	0.1325* (0.030-0.500) (IV)	-
Pethidine	1 (0.6)	0.025 (IV)	-
Tricyclic antidepressants	3 (1.8)		
Amitriptyline	2 (1.2)	-	17.5 (10-25)
Nortriptyline	1 (0.6)	-	10

Abbreviations: IV; intravenous injection, IM; intramuscular injection
*IV form of lorazepam is unavailable in Thailand

TABLE 4. First medications prescribed by attending physicians for initial management of agitation, classified by working diagnoses made by attending physicians and final diagnoses made by consultant psychiatrists.

Cause of agitation	N	First medications prescribed by attending physicians for initial management of agitation							
		Benzodiazepine		Antipsychotics		Opioid		TCA*	
		n	%	n	%	n	%	n	%
All causes	188	112	59.6	42	22.3	9	4.8	3	1.6
Delirium due to a medical condition									
Working diagnosis	50	18	36.0	23	46.0	4	8.0	-	-
Final diagnosis	89	32	36.0	37	41.6	7	7.9	2	2.2
Alcohol withdrawal delirium									
Working diagnosis	21	19	90.5	2	9.5	-	-	-	-
Final diagnosis	55	51	92.7	1	1.8	-	-	-	-
Alcohol withdrawal									
Working diagnosis	71	58	81.7	4	5.6	1	1.4	1	1.4
Final diagnosis	27	20	74.1	2	7.4	-	-	-	-
Other psychiatric disorders**									
Working diagnosis	12	4	33.3	3	25	1	8.3	-	-
Final diagnosis	9	3	33.3	2	22.2	1	11.1	1	11.1

*TCA; tricyclic antidepressants

**Other psychiatric disorders include schizophrenia, adjustment disorder, brief psychotic disorder, bipolar disorder, major depressive disorder and dementia

precipitate agitation.[10,15] Misdiagnosing medical conditions as psychiatric disorders can lead to lethal consequences as the underlying causes of agitation remain uncorrected.[15] Consistent with other reports[16,17], delirium was a common diagnosis in patients referred for a psychiatric consultation. In this study, almost half of the cases suffered from delirium due to general medical conditions and around one-third had AWD.

Of equal importance is the burden that agitation can add to hospital costs and human resources. One study reported that among general hospitals, the presence of agitation significantly increased the length of stay and increased total hospital costs by 8%.[18] Thus, it is imperative that HCPs are properly trained to identify and manage agitation to prevent the escalation of symptoms and reduce the use of coercive measures such as physical restraints and involuntary medication, which can lead to complications.[19]

Interestingly, one-third of agitated patients first manifested with a cognitive symptom, "confusion", but more easily noticeable physical symptoms such as fidget were the main reason for psychiatric consultation. This reflects how agitation is a heterogeneous and complex symptom that can start as mild confusion and may spiral to violence. Therefore, HCPs need to understand the course of agitation and its capacity to deteriorate so timely diagnosis can be made. Our findings suggest that physicians should remain vigilant for agitation, especially in the first three days after admission. Additionally, medications should be reviewed to reduce the use of polypharmacy and avoid drugs that may induce or worsen agitation. The prevention and early detection of agitation can reduce adverse outcomes, shorten the length of hospital stay, and decrease hospital costs.[9,20]

There was a low concordance between AP and psychiatrist diagnoses of delirium, AWD, and AW. This confirms a previous finding that agitation may hinder the diagnosis of delirium[21] and makes it more difficult for physicians to correctly diagnose the condition.[22] Our findings demonstrated that 22.5% of patients with

delirium due to medical conditions were misdiagnosed as AW and AWD. This led to 36.0% patients with delirium receiving benzodiazepines instead of antipsychotics in this study, which is of concern as benzodiazepines lack evidence in the management of non-alcohol-related delirium[23] and can worsen delirium.[24] Our findings underline the need for a thorough history and physical examination to differentiate delirium due to another medical condition from alcohol withdrawal syndrome.

Furthermore, 5.6% of our patients with delirium were misdiagnosed as having other psychiatric disorders. This may be because delirium often presents with psychiatric symptoms, such as hallucination, illusion, and delusion[16,25] and some physicians may consider delirium as a psychiatric condition instead of a complex manifestation of medical conditions. This finding is significant in drawing attention to the importance of specific guidelines for HCPs and a need for improved knowledge and skills in diagnosing delirium.

Only one patient received verbal de-escalation as an initial management. Verbal de-escalation may remove the need for invasive management in a substantial number of patients, training in verbal de-escalation skills among HCPs should be considered. Nearly 60% of all cases were physically restrained. Moreover, some patients were physically restrained without sedating medications or verbal de-escalation, which previous researches suggest can result in physical and psychological injuries.[14,26] A recent study showed that a minority of health care providers acknowledged their hospital policy on restraint use.[26] These findings support the need for locked/seclusion rooms, and improved knowledge about proper indications, monitoring and documentation of restraint use. Many physicians resorted to using sedative medications, with most cases receiving intravenous diazepam injection. This is a concern given the long half-life, drowsiness and respiratory-depression effect.[13]

Less than half of patients with delirium were appropriately given antipsychotics, but more than one-third were given benzodiazepines. APs prescribed benzodiazepine to ameliorate agitation in 36.0% of patients with the WD of delirium before psychiatric consultation. This suggests that inappropriate pharmacological intervention was not only due to misdiagnosis, but also due to a deficit in knowledge of delirium management. In this study, 7.3 % of patients diagnosed with AWD, a life-threatening condition, were not prescribed with benzodiazepine which is the gold-standard treatment.[27] These findings are alarming and suggest that agitation management guidelines are needed.

CONCLUSION

We observed that medical conditions, rather than psychiatric conditions, were the source of agitation in the majority of patients. There was significant disagreement between APs and psychiatrists regarding the diagnoses, and an over-reliance on physical restraints and parenteral benzodiazepine injection for management.

Clinical application

These findings highlight a role for education and training on the detection and management of agitation, especially the use of non-coercive measures and appropriate use of sedative medications. We also recommend the construction of seclusion rooms within major inpatient units that currently have a high prevalence of agitated patients so that de-escalation can be done effectively.

Recommendation for further study

Future work should concentrate on the development of guidelines on agitation in general hospitals with limited resources.

Limitations

Our research has several limitations and the results should be interpreted with caution. First, information was drawn from one hospital limiting the generalizability of the research. Given that there are no psychiatric wards or seclusion rooms in the study hospital, there is a possibility that limited resources may have influenced how patients were managed. Second, due to the retrospective methodology, there may be variation in diagnoses or symptoms classification, incomplete documentation of non-pharmacological management, and subjective evaluation. Third, only data of patients referred for a psychiatric consultation were collected. Mildly agitated patients may have been successfully managed without psychiatric consultation.

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Correlation of Moral Courage and Organizational Commitment in Operating Room Nurses

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ABSTRACT

Objective: Moral courage distinguishes real moralists from hypocrites and indicates the commitment of nurses to their patients. Organizational commitment can also influence this commitment. Therefore, the present study aimed to investigate the correlation between moral courage and organizational commitment of operating room nurses working in the teaching hospitals of Arak University of Medical Sciences.

Methods: This cross-sectional correlational study was conducted on 136 operating room nurses who were selected using the convenience sampling method. The required data were collected through demographic information form, the organizational commitment questionnaire of Allen and Myer, and the professional moral courage scale by Sekerka and colleagues. The collected data were analyzed using SPSS (version 21) for descriptive and correlational analyses.

Results: The mean scores of moral courage of operating room nurses were 62.5±6.5 and in 101.86±13.7 organizational commitment. Moreover, moral courage did not have a statistically significant relationship with organizational commitment (P>0.05). The moral courage and organizational commitment of the participants differed significantly in terms of their type of employment (P<0.05) and age (P<0.05).

Conclusion: Given the high mean score of moral courage and organizational commitment in operating room nurses, it can be said that nurses tend to show moral behaviors. On the other hand, the low score of the endurance of threat indicates that operating room nurses do not receive the necessary support from the organization for their courageous behavior. Therefore, the support of senior managers is essential for the occurrence of such behaviors.

Keywords: Nursing ethics; moral obligations; efficiency organizational; operating room nursing; courage (Siriraj Med J 2021; 73: 183-190)

INTRODUCTION

Employees are the backbone of the organizations and hospitals.The nurses play a very important role in the improvement of health productivity.[1] The sensitivity of this role is even more clear in the operating room since the provision of quality care to unconscious patients requires a high level of commitment. Operating room nurses have delicate responsibilities as members of the treatment team.[2] Respect for the basics and values, commitment to the organization, and adherence to professional and ethical principles are more essential, sensitive, and important in this profession.[3] However, mostly due to their increasing responsibilities and patients number, social justice, access to healthcare services limitations

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and personal or organizational barriers prevent them from doing moral behavior easily and poses challenges to them regularly.[2,4]

The operating room is a delicate yet stressful environment. Interpersonal conflicts are common in this environment and avoiding them requires management planning and adherence to ethical solutions. Congestion, congestion, work pressure, insomnia and fatigue, stress Unwanted actions cause challenges such as moral distress. One of the influential factors in nurses' decision-making in the face of this moral distress is moral courage and commitment.[5] These moral characteristics create moral comfort and increase professional solidarity in the practice.[3] Moral courage motivates nurses to do the right thing and accept the consequences, even if it is difficult for them.[6] Sekerka (2009) defines the five aspects of moral courage as 1) moral agency which is the desire to show moral behavior and have a strong will to do the right thing, 2) multiple values which refers to the ability to use multiple values in the process of making a moral decision and adherence to one's beliefs despite external desires or demands, 3) endurance of threat which means showing moral behavior despite real or imaginary dangers or threats, 4) going beyond compliance which indicates that a person should pay attention to the rules and their purpose, and also go beyond the limits of obedience to do the right, logical, or appropriate thing, and 5) moral goal which means having the motivation to perform tasks that require making decisions that are accompanied by virtues such as forethought, honesty and justice.[7] Proper moral performance of operating room nurses and their commitment to the patients require considerable moral courage.[8]

Organizational commitment means the individual's desire to continue working and serving in an organization, so that the organization becomes part of their identity.[9] According to McQuarrie (2004), the organizational commitment of employees depends on various factors, such as individual, occupational, organizational, and extra-organizational factors.[10] Investigation of the influential factors on organizational commitment can help an organization improve its performance and attract capable employees. In this regard, moral courage is one of the individual factors that can affect organizational commitment.[11]

Allen and Mayer (1998) proposed a three-part organizational commitment model.[12] In this model, commitment determines the relationship between the individual and the organization and consists of three aspects, namely 1) affective commitment which means emotional attachment of the employees to the organization that gives them a sense of identity and keeps them involved, thereby employees with this type of commitment tend to stay in the organization, 2) continuance commitment that refers to the imagined cost of leaving the organization, and 3) normative commitment that indicates staying with the organization as the duty of someone who is a part of that organization.[12,13] Organizational commitment has a great impact on the efficiency and productivity of an organization.[14] People with higher organizational commitment show less absence, delay, and tendency to leave, have a better performance, and are more enthusiastic.[15]

In today's world, the individual performance of employees is affected by ethical issues and human interactions that should be prevalent in organizations.[16] Nurses face challenges when they are unable to do their job properly due to structural and internal constraints. One of these challenges is moral distress, in which it is not possible to achieve the intended moral goals.[2]

The reason for such ethical challenges is considered to be the decline in the quality of care provided and insufficient support, which can put nurses at risk and confront them with moral conflict.[17] Nurses in the face of these conditions, according to the extent Organizational commitment as a mediator may react differently, for example, becoming indifferent to circumstances and avoiding appropriate services.[18] Organizational commitment as a mediator can affect the effectiveness and quality of services. On the other hand, nurses need courage in ethical practice to overcome their personal fears. Therefore, for nurses who have courageous moral performance.[19] Commitment to the patient is more important than the concerns they may have about their own risk.[20] Given that the operating room is one of the most essential, useful and common clinical space, it is a meeting place for professionals and professionals who provide vital services and care to a wide range of patients in a coordinated team. One of the important components of operating room nurses is the category of moral decision making, which has moral courage and professional commitment that makes moral decision making stronger.[21] also due to lack of enough studies conducted on moral courage and organizational commitment, the present research aimed to determine the correlation between moral courage and organizational commitment of nurses in operating rooms affiliated with Arak University of Medical Sciences, Iran, in 2019.

MATERIALS AND METHODS

This cross-sectional-correlational study was conducted on all of 136 operating room nurses who worked in the operating rooms affiliated Arak University of Medical Sciences. Purposeful sampling was done. After obtaining

permissions, the researcher referred to the operation rooms of hospitals. Informed consent was obtained from nurses and they were assured that the information in this questionnaire will remain anonymous and confidential. researcher distributed questionnaire among the operating room nurses. The researcher was ready to answer any ambiguities in the questions. The participation in the study is voluntary for nurses and fortunately, all of them were willing to participate in the study and respond rate was 100%.

The inclusion criteria consisted of the educational level of high school and above as well as ≥6 months of work experience. The data collection tool was a three-part questionnaire.The first part was the demographic information of the participants, which included age, sex, education, work experience, employment status and marital status. Because there was no nurse with widowed and separated marital status in the study, marital status was divided into two groups: married and single.

The variables of age and work experience were collected qualitatively, so each of them was classified into four groups. **Permanent employment**, means employees who have very high job security, are employed to hold government responsibilities and are legally under the supervision of the country›s employment system. In **temporary –to permanent employment**, individuals are subject to a contract under which they are employed in a government agency, which allows them to be formally employed if they continue and are satisfied with their performance. **Recruitment plan employment**, also includes graduates of clinical disciplines who are required to work for double the length of their studies in educational and medical centers, with certain salaries and benefits. In **under –a-contract employment**, individuals under a contract who have certain rights and duties must work temporarily at that center for a certain period of time.

The second part of the questionnaire investigated moral courage by using the professional moral courage questionnaire designed by Sekerka and colleagues (2009). This questionnaire contains 15 phrases regarding the five dimensions including ,moral agency, multiple values, endurance of threats, going beyond compliance, and moral goals, each of which includes three separate questions.[7] This questionnaire was scored based on a Likert scale from 1 (never) to 5 (always). Therefore, the total score of the questionnaire ranged from 15 to 75 and the moral courage score was the mean of the scores of all the phrases. In a study conducted by Mohammadi and colleagues.[22] the content validity index of this questionnaire was obtained at 81% and the Cronbach's alpha was calculated at 0.85. Therefore, after obtaining permission from Mohammadi and colleagues, the same version of the questionnaire was used in the present study.[22] Cronbach's alpha was measured again in the present research using a sample of 20 people which was obtained at 0.77, 0.83, 0.71, 0.7, 0.84 regarding the aspects of moral agency, multiple values, endurance of threats, going beyond compliance, and moral goals, respectively. Furthermore, the total Cronbach's alpha coefficient was obtained at 0.78.

The third part of the questionnaire consisted of the standard questionnaire of organizational commitment designed by Allen and Myer (1990) and contains 24 items.[12] The validity of this questionnaire was confirmed in a study by Dehghani and colleagues (2015).[23] The same version of this questionnaire was used in the present study with a permission of the researcher. Moreover, the reliability of the questionnaire was confirmed using a sample of 20 nurses and the Cronbach's alpha coefficient was obtained 0.72 for continuance commitment, 0.8 for affective commitment and 0.71 for normative commitment, respectively. Furthermore, the total Cronbach's alpha coefficient was obtained at 0.76. This questionnaire measures the organizational commitment and is scored based on a Likert scale from 1 (strongly disagree) to 7 (strongly agree). This questionnaire consisted of 24 items which were divided into three subscales, namely continuance commitment (8 items), affective commitment (8 items), and normative commitment (8 items).[12]

The required permissions for the conduction of the research were obtained from the Research Deputy and Arak University of Medical Sciences and hospitals (IR.ARAKMU.REC.1398.092). The ethical considerations were respected since the purpose of the study was explained to all the participants and they were assured that their information would be kept confidential. Therefore, the published data were kept confidential and in compliance with publication ethics. Also, the participation of nurses in the study was voluntary and if they did not want to participate in the study or did not want to continue to cooperate, they could leave in the study freely without any consequences. Data were collected from all hospitals in 30 days. Collected data were analyzed in SPSS software (version 21) using, descriptive statistics contain frequency, frequency percentage, mean, standard deviation, and statistical tests contain Pearson correlation coefficient test, one-way analysis of variance, and independent t-test. The Kolmogorov-Smirnov used to test normal distribution.

RESULTS

Most age category of nurses were within 31-40 years and in 8-14 their work experience category. (The

variables of age and work experience were qualitatively collected in four groups). The range of participant's age was 20-59 years. The minimum and maximum work experience of the participants was 1-30 years. In total, 136 nurses participated in this study, 87.5% of whom were female. Moreover, 68.4% of them were married, while 31.6% were single. The mean score of the moral courage in operating room nurses was 62.5±6.5 which is considered a high level. Furthermore, the mean score of the organizational commitment was 101.86±13.7 which is considered high as well.

There was a significant relationship between the mean score of the aspects of moral courage and the type of employment (P<0.05), so that the mean scores of the aspects of the endurance of threat, going beyond compliance, and the lowest of moral goals were contractual employment and highest in the formal employment groups. In addition, the scores of different age groups regarding the affective aspect of the organizational commitment had a significant difference with each other (P<0.05). The most scores of affective commitment were observed in the age ranges of 20-30 and the least in the 40-50 years. Table 1 shows a summary of the demographic information of the participants and the mean score of moral courage and organizational commitment.

Among the various aspects of moral courage, the highest and lowest mean scores were observed in moral agency (13.76±1.63) and endurance of threat (11.32±1.89). Furthermore, regarding organizational commitment, the highest mean scores of continuance commitment were perceived (36.21±8.02) and lowest in (31.50±5.35) affective aspects. Table 2 shows the collected data on the aspects of moral courage and organizational commitment. There was no significant relationship between the moral courage and organizational commitment of operating room nurses (P>0.05). Moreover, no significant relationship was detected between the various aspects of moral courage and those of organizational commitment (P>0.05). The correlation coefficient of the relationship between the aspects of moral courage and those of organizational commitment of operating room nurses is shown in Table 3.

DISCUSSION

In the present study, the mean score of moral courage in the operating room nurses was high. This finding is consistent with the results of previous studies conducted in Iran.[24] However, the obtained score of moral courage was low in a study performed by Day (2007).[25]

The discrepancy between the results of this study and the Day study helps us to know that the type of work environment, moral climate of the medical center, organizational culture and the level of support of managers and organizations for nurses, can play a very important role in increasing moral courage.[26] Therefore, the high score of moral courage of operating room nurses in this study indicates that they always act based on the best scientific interest and the best rational needs of patients.

Regarding moral courage, the highest mean scores were observed in moral agency and the lowest in endurance of threat. In previous studies[27,28] on moral courage, the lowest mean score was observed in the endurance of threat, which is consistent with the results of the present study. Low endurance of threat is of great importance since the organizational factors and performance of the people working in operating rooms can have a great impact on the behavior of nurses and pose ethical challenges and dilemmas to them. Operating room nurses see themselves as moral agents and tend to show moral behaviors that are associated with virtues, such as forethought, honesty, and justice. However, the pressure and fear of moral challenges reduce their endurance of threats. The low score of this aspect could indicate that nurses do not feel supported by the organization for their courageous behavior.

The mean score of organizational commitment in operating room nurses was high which was consistent with the results of the studies performed by Azari and colleagues[29] and Khosravani and colleagues[15] in Amol, Iran. However, according to the findings of the majority of previous studies[30-34] the organizational commitment of nurses was moderate. This inconsistency could be due to a variety of factors, such as differences in working conditions, work environments, organizational rules and regulations, and the level of awareness of nursing managers regarding the ways to improve organizational commitment.

The highest mean scores of organizational commitments in operating room nurses were observed in the continuance and lowest in affective commitment. Based on the findings of the study performed by Khosravani and colleagues[30] the highest mean score was observed in the aspect of affective commitment which is not consistent with the results of the present study. The finding of the present research could be due to the desire of nurses to remain a member of the organization regarding their awareness of the cost of leaving it since they need their job and if they leave it, they will lose everything. Low mean score of affective commitment indicates their lower attachment to the organization which means that they are only motivated to work in that organization since they do not have better job opportunities.

TABLE 1. Mean scores of moral courage and organizational commitment of participants according to their demographic characteristics.

Variable		Number (%)	Average score ± standard deviation of moral courage	Average score ± standard deviation of organizational commitment
Work experience	Less than 5 years	52 (38.2)	62.28 ± 6.30	105.05 ± 9.41
	8-14 years	61 (44.9)	62.14 ± 6.72	100.21 ± 14.70
	15-22 years	14 (10.3)	63.71 ± 6.78	96.29 ± 11.38
	23-30 years	9 (6.6)	63.66 ± 6.83	103.33 ± 25.73
	total	136 (100)	62.47 ± 6.52	101.87 ± 13.78
Statistics			ANOVA	ANOVA
P - value			0.81	0.11
Marital status	Married	93 (68.4)	62.11 ± 6.76	102.27 ± 14.11
	Single	43 (31.6)	63.20 ± 6	100.97 ± 13.12
Statistics			T - test	T - test
P - value			0.37	0.61
Education Status	Diploma	1 (0.7)	59 ± 0	112 ± 0
	Associate	40 (29.4)	61.36 ± 7.02	102.15 ± 14.22
	Bachelor	91 (66.9)	63.14 ± 6.30	101.76 ± 13.24
	Master	4 (2.9)	59 ± 5.71	99 ± 24.5
	Total	136 (100)	62.47 ± 6.52	101.87 ± 13.78
Statistics			ANOVA	ANOVA
P - value			0.32	0.87
Age	20 – 30	55 (40.4)	62.66 ± 6	104.43 ± 9.30
	31 – 40	62 (45.6)	62.12 ± 7.10	100 ± 14.83
	41 – 50	13 (9.6)	63.92 ± 6.67	98.53 ± 16.84
	51 years and up	6 (4.4)	61 ± 5.32	104.83 ± 25.90
	Total	136 (100)	62.47 ± 6.52	101.87 ± 13.78
Statistics			ANOVA	ANOVA
P - value			0.76	0.25
Gender	Female	119 (87.5)	62.87 ± 6.48	101.74 ± 14
	Male	17 (12.5)	59.64 ± 6.39	102.70 ± 12.39
Statistics			T - test	T - test
P - value			0.057	0.79
Employment Status	Permanent	62 (45.6)	64.04 ± 6.37	98.82 ± 16.73
	Under-a-contract	6 (4.4)	55.67 ± 5.69	107.83 ± 15.11
	Temporary-to permanent	22 (16.2)	60.13 ± 6.24	104.04 ± 10.26
	Recruitment plan	46 (33.8)	62.3 ± 6.22	104.15 ± 9.47
	Total	136 (100)	62.47 ± 6.52	101.87 ± 13.78
Statistics			ANOVA TUKEY HSD	ANOVA TUKEY HSD
P - value			0.04	0.11

TABLE 2. Mean score of aspects and total score of moral courage and organizational commitment of operating room nurses.

	Dimensions	Frequency	Lowest score	Highest score	Mean	Standard deviation
Moral courage	Moral agency	136	4	15	13.76	1.63
	Multiple values	136	7	15	12.54	1.90
	Endures threat	136	5	15	11.32	1.89
	Goes beyond compliance	136	6	15	11.96	2.03
	Moral goal	136	6	15	12.88	1.78
	Total moral courage	136	46	75	62.46	6.53
Organizational Commitment	Affective	136	12	44	31.50	5.35
	Continuance	136	11	56	36.21	8.02
	Normative	136	12	53	34.15	5.97
	Total organizational commitment	136	36	145	101.86	13.77

TABLE 3. Correlation coefficient of the relationship between the aspects of moral courage and those of organizational commitment in operating room nurses.

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
1. Affective										
2. Continuance	.226**									
3. Normative	.299**	.237**								
4. Total organizational commitment	.649**	.773**	.688**							
5. Moral agency	-0.06	-0.05	-0.01	-0.06						
6. Multiple values	-0.05	0.04	0.04	0.02	.281**					
7. Endures threat	-0.15	-0.06	0.08	-0.06	.200*	.385**				
8. Goes be yond compliance	-0.06	-0.08	-0.06	-0.09	.283**	.361**	.468**			
9. Moral goal	-0.12	-0.07	0.09	-0.05	.326**	.379**	.475**	.520**		
10. Total moral courage	-0.12	-0.06	0.04	-0.07	.567**	.689**	.728**	.765**	.765**	

Note: N= 136, * p<0.05, ** p<0.01

In line with the findings of the present study, the results of another study which was conducted in Iran (2015) indicated that there was no significant correlation between moral courage and organizational commitment in operating room nurses.[35] However, according to the results of another study conducted by Mokhtaran (2015) in Iran, courage, as one of the aspects of the performance of managers, has the most positive and significant effect on the organizational commitment of the employees.[36] In justification of this finding, it can be said that moral courage, as a personality trait, is one of the foundations of one›s personality and is a management virtue that is a precursor to professional ethics behavior in organizational environments.[11] On the other hand, organizational commitment is an important job and organizational attitude and is mostly influenced by social and organizational factors such as professional ethics. Many studies have shown that organizational commitment has a positive and significant relationship with professional ethics.[29,31,37] Oka and Wayne›s research shows a positive and significant relationship between professional ethics and organizational commitment.[38] Thus, social factors such as organizational commitment are not directly related to individual factors such as moral courage.[29]

According to the results, moral courage had a significant relationship with only one of the demographic characteristics which is the type of employment. Moreover, people who are formally employed show greater moral courage in terms of going beyond compliance, moral goals, and endurance of threats, compared to the contractually employed group. This finding was consistent with that of the studies performed by Aultman and Marry.[39] According to Baringher,[40] some nurses show moral courage despite their young age, low work experience, and type of employment; however, generally, older age and formal employment increase job security, decisive behaviors, and moral courage in nurses.

CONCLUSION

The high score of average moral courage and organizational commitment of operating room nurses indicates the good implementation of ethical principles and culturally respected values of patients in the operating room. The low score of the threat tolerance variable indicates that operating room nurses do not feel the necessary support for managers for their courageous behavior.[41] Therefore, the support of senior managers in this area is essential. Considering the significant relationship between moral courage and the type of employment, it is suggested that nursing managers use the results of this study in their decisions and prioritize the stability and certainty of nurses› employment in their planning and the use of experienced nurses put. To increase nurses ‹emotional commitment, it is recommended that managers use factors that increase nurses› motivation, such as encouraging behaviors, increasing occupational safety and health, clarifying responsibilities, and properly evaluating staff performance.

Du to using the self-report questionnaire the results of the study depend on nurses' understanding of the concept of moral courage and organizational commitment. To overcome this limitation, these concepts were first explained to them before distributing the questionnaire. Finding of a study can use in the nursing education for developing the content of nursing curricula and in planning to development of nurses' moral courage and organizational commitment.

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Comparison of the Outcomes between Ultrasound-guided PCNL in Lateral Position and Open Nephrolithotomy for Patients with Staghorn Renal Stones

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ABSTRACT

Objective: To compare the clinical outcomes of ultrasound-guided percutaneous nephrolithotomy (US-PCNL) in lateral position and anatrophic nephrolithotomy (ANL) in the treatment of staghorn renal stones.

Methods: Between October 2016 and July 2020, individuals with staghorn renal stones undergoing an operation at Buri Ram Hospital in Thailand were included in this study. They were divided between group I (patients undergoing US-PCNL, n=114) and group II (patients undergoing ANL, n=112). The outcomes regarding stone-free rate (residual stone less than 4mm with asymptomatic), the stone clearance rate (the elimination rate of total stone surface after the operation), operative times, length of hospitalization, and complications were collected and analyzed.

Results: The patient's demographics and stone characteristics were not significantly different between the two groups, except that more preoperative hydronephrosis was found in the ANL group (78.6% vs. 53.5%, $p<0.001$). Regarding the primary outcome, the stone-free rate was significantly lower in the US-PCNL group (47.4% vs. 75.9%, $p<0.001$), whereas the stone clearance rate was not significantly different (96.4±6.0% in the US-PCNL group and 97.7±5.8% in the ANL group, $p=0.098$). No difference was found according to the major and minor complications between the US-PCNL and ANL groups; however, the US-PCNL group had a significantly lower transfusion rate than the ANL group (3.5% vs. 17.9%, $p<0.001$). The total operative time in both groups was not different; however, the length of hospitalization for the US-PCNL was significantly shorter than for the ANL group (10.0 vs. 12.9 days, $p=0.002$). A multivariate analysis revealed that the operative method was a significant factor associated with the stone-free rate (OR=5.96, 95%CI=3.06-11.62, $p<0.001$), blood transfusion (OR=5.75, 95%CI=1.84-18.03, $p=0.003$), and the length of hospitalization (F=10.27, $p=0.002$); while the percentage of stone clearance were not statistically different between the two operation methods (F=2.76, $p=0.098$).

Conclusion: The ANL had a higher stone-free rate for patients with staghorn stones; however, the stone clearance rate was not significantly different between the US-PCNL and ANL groups. The advantages of the US-PCNL over the ANL were less blood transfusion and shorter length of hospitalization, while the complications were not significantly different between the two operative methods.

Keywords: Staghorn renal stone; ultrasound-guided percutaneous nephrolithotomy; anatrophic nephrolithotomy; lateral position (Siriraj Med J 2021; 73: 191-197)

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INTRODUCTION

Renal stones are a common disease, especially in the northeast and the north of Thailand. At Buri Ram Hospital, we are familiar with anatrophic nephrolithotomy (ANL) for staghorn renal stones treatment. ANL was once considered as the "gold standard" for the treatment of staghorn renal stones and it was used as the benchmark for other treatment. An excellent stone-free rate can be achieved with ANL; therefore, ANL is still the operation of choice for large stone treatment in some regions in the world.[1] Currently, percutaneous nephrolithotomy (PCNL) is the main surgical treatment for large renal stones. Most urologists are familiar with the use of fluoroscopy guidance during the percutaneous renal access; however, radiation exposure from fluoroscopy might cause potential long-term adverse effects for patients and medical personnel.[2] Given the concerns regarding cumulative radiation effects, ultrasound (US)-guided renal stone access is a reliable alternative imaging method to PCNL for avoiding ionizing radiation exposure.[3] Interestingly, US-guided renal stone access has not been adopted worldwide; this technique has been widely used only in Asia.[4-8] We have successfully performed US-guided PCNL (US-PCNL) in our hospital for renal stone treatment since 2014. However, the most appropriate treatment option for staghorn renal stones is still under debate, and some authors suggest that open renal stone surgery, such as ANL, should be used for staghorn renal stones.[9,10] There have been several comparative studies that have presented the outcomes of fluoroscopic-guide PCNL; however, there are few studies analyzing the outcomes of US-PCNL for the treatment of staghorn renal stones.[9] Therefore, the objective of this study is to compare the treatment outcomes of US-PCNL with ANL.

MATERIALS AND METHODS

This historical cohort study was conducted at Buri Ram Hospital, Buri Ram, Thailand. All of the studied patients were operated on by three board-certified urologists who had more than 3 years of experience in US-PCNL. After the study was approved by the ethics committee of Buri Ram Hospital (BR 0032.102.1/40) and registered in the Thai Clinical Trials Registry (TCTR20200806002), the clinical data of all the patients that were diagnosed with staghorn renal stones larger than 2.5 cm and requiring treatment with US-PCNL or ANL from October 2016 to July 2020 were collected. The size of the stones was maximum stone length in preoperative plain film radiograph of the kidneys, ureters, and bladder (KUB) and the degree of hydronephrosis was evaluated by imaging studies which included intravenous pyelography, ultrasonography, or computed tomography. Patients who loss to follow-up after 3 months were excluded.

Based on the data of previous study, which reported a 61% stone free rate in the ANL group and 41% in US-PCNL group[9], the sample size was calculated using a power of 90% and a significance level of 0.05. Our sample size calculation revealed a minimum sample size of 103 patients in each US-PCNL group and ANL group with an additional 10% of subjects in order to accommodate the projected dropout rate. A total of 226 patients that met the criteria were enrolled. One hundred and fourteen patients that had undergone US-PCNL were categorized into group I and 112 patients that had undergone ANL were categorized into group II.

Surgical technique

Group I (US-PCNL)

Under general anesthesia, a 5 French ureteral catheter was placed via a rigid cystoscope in the lithotomy position in all PCNL patients. Percutaneous access was performed in a lateral position. The stone position was identified using ultrasound. We gave the patients normal saline via a ureteral catheter for artificial hydronephrosis if the pelvicalyceal system of the kidneys was not dilated. Renal puncture was carried out with an 18-gauge needle under an ultrasound needle guide. Alken's coaxial telescopic metal dilators were used to dilate the tract up to 27 French size over a guide-wire; then a 30 French Amplatz sheath was placed for the percutaneous access port. A 26 French rigid nephroscope was applied and the stone was disintegrated with an ultrasonic and pneumatic lithotripter. For the complex staghorn renal stones occupying several calyces, a second tract was created using the same technique. A nephrostomy tube was placed at the end of the operation for 24 to 48 hours.

Group II (ANL)

Under general anesthesia, a flank incision was performed in a lateral position. Gerota's fascia and perinephric fat were carefully dissected off the renal capsule. The renal artery and vein were identified and cross clamped with Satinsky's vascular clamps. Sterile iced slush normal saline was packed into the perirenal space in order to maintain regional hypothermia after the renal vessels were occluded. The kidney was incised at the lateral border along Brodel's line and the stones were removed. Renal parenchyma and calyces were repaired with 3-0 chromic catgut. The renal capsule was closed with 2-0 chromic catgut.

The stone-free rate was evaluated 3 months after surgery with a plain KUB film. The results were classified

as stone free status, clinically insignificant residual stone fragments (CIRFs) ≤ 4 mm, nonobstructive, noninfectious, and asymptomatic.[11] The stone clearance rate was defined as the elimination rate of total stone surface after the operation. Other outcomes including total operative time, length of hospitalization, blood transfusion, and complications (grade I-V according to Clavien-Dindo classification)[12] were collected and analyzed.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (range) and analyzed between group I and group II by using a t-test or the Mann-Whitney U test. The categorical data were expressed as number and percentage and were compared using a chi-squared test or Fisher's exact probability test. Factors potentially associated with the operative outcomes were included in a multivariate model of logistic regression to test their prediction on stone-free status and blood transfusion. The odds ratio (OR) with 95% confidence intervals (95%CI) for each variable was determined. In addition, this study used a multivariate analysis of variance (MANOVA) to test the differences between the two operative methods on the two key operative outcomes which were the stone clearance rate and the length of hospitalization. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 226 patients were included, with US-PCNL performed on 114 patients and ANL performed on 112 patients. The patient demographics and stone characteristics of the US-PCNL and ANL groups were similar except that the preoperative hydronephrosis was higher in the ANL group, as summarized in Table 1.

The operative outcomes were shown in Table 2. In terms of the primary outcome, the stone-free rate was significantly lower in the US-PCNL group (47.4% in the US-PCNL group and 75.9% in the ANL group, $p<0.001$), whereas the stone clearance rate was not significantly different between the two groups (96.4±6.0% in the US-PCNL group and 97.7±5.8% in the ANL group, $p=0.098$). The US-PCNL group exhibited a significantly lower transfusion rate than the ANL group. The total operative times for both groups were not different, but the average length of hospitalization for the US-PCNL was significantly shorter than for the ANL group. There was no significant difference in the major and minor complications according to the Calvien-Dindo classification between the groups, as summarized in Table 3. A multiple logistic regression showed that the operation method was a significant factor associated with stone-free status and blood transfusion. The odds of the patients who undergone ANL method to obtain a stone free status were 5.96 times greater than the odds of those who undergone US-PCNL method (OR=5.96, 95%CI=3.06-11.62, $p<0.001$). On the other hand, the odds of the patients who undergone ANL method to received blood transfusion were 5.75 times higher than those who undergone US-PCNL method (OR=5.75, 95%CI=1.84-18.03, $p=0.003$) as shown in Table 4, 5. A multivariate analysis of variance (MANOVA) was used to test the effect of operative methods on stone clearance rate and length of hospitalization. The multivariate test using Pillai's criterion revealed a significant main effect of operation methods on dependent variables (MANOVA: F=6.61, $p=0.002$). The univariate tests showed that the patients who undergone US-PCNL method had significantly shorter length of hospitalization than those who undergone ANL method (F=10.27, $p=0.002$) while the percentage of stone clearance were not statistically different between the two operation methods (F=2.76, $p=0.098$) as summarized in Table 6.

DISCUSSION

Staghorn renal stones are defined as stones that mandatorily fills the renal pelvis with an extension that branch into at least one caliceal group, and it may lead to the deterioration of renal function and life-threatening urosepsis.[13] Complete stone removal is an important therapeutic goal in order to eradicate further infection, urinary tract obstruction, and recurrent renal stone formation. Complete stone removal is also crucial for the preservation of kidney function.[14] ANL is one of the best options for staghorn stone removal and is considered the benchmark for other treatments because of the high stone elimination rate[9,10]; however, there is a possibility for reduction in renal function due to parenchymal incision and ischemic injury.[1] Currently, most patients with staghorn renal stones can be managed using minimally invasive surgery such as PCNL. Fluoroscopic guidance is the mainstay imaging for the renal access step in PCNL, but it can cause radiation exposure in patients and medical personnel.[3] Ultrasound guidance is a reliable alternative type of imaging for direct PCNL. It can minimize radiation exposure and there is no need for contrast media. Moreover, it can prevent adjacent visceral organ injury and can be performed in any patient position.[2] However, the absence of staghorn stones has been associated with successful US-PCNL[2] as the ideal candidate for US-PCNL is a generally healthy, non-overweight patient with at least moderate hydronephrosis in non-staghorn renal stones on imaging.[15]

TABLE 1. Demographic characteristics of the patients in the US-PCNL and ANL groups.

	Group I US-PCNL (n=114)	Group II ANL (n=112)	*p*-value
Mean age, year	56.4 ± 10.1	53.7 ± 12.3	0.069
Gender			
Male sex no. (%)	69 (60.5)	59 (52.7)	0.234
BMI, kg/m^2	23.4 ± 3.2	22.9 ± 4.2	0.289
Laterality			
Right side no. (%)	57 (50.0)	67 (59.8)	0.138
Stone length, mm	55.3 ± 12.9	58.2 ± 22.4	0.236
Stone surface area, mm^2	1677.4 ± 781.8	1885.2 ± 1284.1	0.144
Preoperative hydronephrosis no. (%)	61 (53.5)	88 (78.6)	<0.001
Preoperative urine culture positive no. (%)	27 (23.7)	22 (19.6)	0.461

TABLE 2. Comparisons of operative outcomes in the US-PCNL and ANL groups.

	Group I US-PCNL (n=114)	Group II ANL (n=112)	*p*-value
Operative time, min	123.1 ± 43.3	133.1 ± 48.7	0.107
Length of hospital stay, days	10.0 ± 6.5	12.9 ± 6.9	0.002
Residual stone > 4 mm, no. (%)	60 (52.6)	27 (24.1)	<0.001
Stone free status no. (%)	54 (47.4)	85 (75.9)	<0.001
Residual stone area, mm^2	69.6 ± 17.5	25.4 ± 4.7	0.016
Stone clearance rates	96.4 ± 6.0	97.7 ± 5.8	0.098
Blood transfusion	4 (3.5)	20 (17.9)	<0.001

TABLE 3. Comparisons of postoperative complications in the US-PCNL and ANL groups.*

	Group I US-PCNL (n=114)	Group II ANL (n=112)	*p*-value
Minor complication (grade I-II) no. (%)	46 (40.4)	59 (52.7)	0.063
Transient fever	45 (39.5)	51 (45.5)	0.357
Failed renal access	2 (1.7)	NA	NA
Minor renal pelvic perforation	1 (0.88)	NA	NA
Serious complication (grade III-IV) no. (%)	6 (5.3)	6 (5.4)	0.975
Visceral organ injury	0	0	
Pneumo/hemothorax	0	0	
Septic shock	5	6	
Postoperative ureteral obstruction	1	0	

*Complications are defined according to Clavien-Dindo classification grade I-V.
Abbreviation: NA = Not applicable

TABLE 4. Multiple logistic regression results for stone free status.

	Odds ratio	95% CI		*p*-value
		Lower	Upper	
Operation (ANL=1, US-PCNL=0)	5.962	3.059	11.620	<0.001
BMI	1.132	1.033	1.241	0.008
Stone size	0.986	0.970	1.003	0.099
Preoperative hydronephrosis (Yes=1, NO=0)	0.329	0.166	0.653	0.001

TABLE 5. Multiple logistic regression results for blood transfusion.

	Odds ratio	95% CI		*p*-value
		Lower	Upper	
Operation (ANL=1, US-PCNL=0)	5.754	1.837	18.030	0.003
BMI	0.954	0.847	1.074	0.435
Stone size	1.003	0.983	1.024	0.745
Preoperative hydronephrosis (Yes=1, NO=0)	1.005	0.359	2.812	0.993

TABLE 6. Multivariate and univariate analysis of variance (MANOVA) results of stone clearance rate and length of hospitalization.

Variable	Multivariate			Univariate					
				% Clearance			Hospitalization		
	F	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
Operation	6.61	0.002	0.006	2.76	0.098	0.012	10.27	0.002	0.044

Several studies have reported successful stone treatment according to the stone free-rate or stone clearance rate.[9,16,17] One of the measures of the stone free rate is by measuring the parameters that are associated with stone burden, including stone diameter, stone surface area, and stone volume.[18,19] Since there are currently no formal guidelines for the assessment of stone burden, in this study, we defined the stone-free rate as having no residual stones or a stone diameter less than 4 mm after the operation, and the stone clearance rate as the ratio of the elimination of the stone surface area after the operation.[11] Our study found that the stone-free rate in the ANL group was significantly higher than in the US-PCNL group (75.9% vs. 47.4%). Our outcomes were similar to the study of Friedrich and colleagues, which reported a 63.7% stone free-rate in open stone surgery and 40.9% stone free-rate in US-PCNL.[9] These results also align with a recent meta-analysis study of the standard PCNL method, which showed a significantly lower stone-free rate in comparison with open renal stone surgery.[10] However, it should be noted that the low stone-free rate in our US-PCNL group was because we did not use fluoroscope to detect residual stones in this group. Fluoroscope was not used in order to avoid radiation according to the as-low-as-reasonably achievable (ALARA) principle.[20] It is worth noting that our US-PCNL patients had a large stone burden (55.3 mm length and 1677 mm^2 surface area) and fewer hydronephrotic kidneys (53.5%). These factors are considered to increase difficulty for US-PCNL.[4]

The stone clearance rate between the US-PCNL and ANL group in this study was not significantly different (96.4±6.0% vs. 97.7±5.8%, p=0.098), which means that the postoperative residual stones in the US-PCNL group were slightly larger than 4 mm and needed only noninvasive auxiliary treatment such as extracorporeal shock wave lithotripsy (ESWL) to achieve stone-free status.

In the present study, the operative time was not significantly different between the US-PCNL and ANL groups (123.1 vs. 133.1 min). The operative time of the US-PCNL in our study was not shorter than open surgery when compared to other studies because we began the operation when the general anesthesia was administered, while several studies usually count the time at the renal access step.[9,17] The US-PCNL patients had a shorter length of hospitalization than the ANL patients (10.0 vs. 12.9 days), which is similar to the study of Chen and colleagues.[10] The overall complications in both groups were not significantly different. The important finding of our study was that the US-PCNL group had a significant lower transfusion rate than the ANL group (3.5% vs. 17.9%, p< 0.001) and no pulmonary or visceral complications were presented in the US-PCNL group. Ultrasonography has the advantage of providing real time visualization of the kidneys and surrounding visceral organs and structures causing a lower risk of pulmonary or visceral complications compare to the standard PCNL. Thus, the US-PCNL method is superior to the standard PCNL method, which is prone to causing complications regarding the surrounding organs.[2,15]

One of the key advantages of this study was an adequate number of participants for achieving a sufficient power for statistical analysis. In addition, our participants' renal stone characteristics and kidney condition differed from previous studies.[14] This research samples were from the northeast of Thailand which associated with a high prevalence of renal stones. Renal stones characteristics found in this region were more complicated because they had large stone burden. In addition, there were lower proportion of hydronephrotic kidney cases which make the surgery more difficult. In this study there were lower proportion of hydronephrotic kidney cases in the US-PCNL group, and there were large stone burden. Thus, the findings of this research are extremely useful

for urologists who are operating in the northeast of Thailand or working with individuals with large stone burdens and non-hydronephrotic kidneys.

Our study had some limitations. First, it is a retrospective study, which may have affected the allocation of the patients to each treatment group. A prospective randomized study should be conducted in order to overcome this limitation in the future. Secondly, the use of stone length and stone surface area to define stone burden is not as accurate as stone volume from computed tomography calculation.[18] However, computed tomography is not available in clinical practice for postoperative stone evaluation because of the risk of radiation exposure and the cost-effective aspect[20], and currently, there are several studies that have used stone length or stone surface area for stone burden estimation.[9,10,16]

CONCLUSION

From our study, it could be seen that US-PCNL is a safe and feasible alternative in comparison with ANL for staghorn renal stone treatment. Although the ANL still had a higher stone-free rate, the stone clearance rate was satisfactory in both the US-PCNL and ANL groups. In addition, there were advantages of the US-PCNL over the ANL regarding less blood transfusion, and shorter length of hospitalization, while the complications were not significantly different between the two groups.

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Comparative Analysis of Effectiveness of Clomiphene Citrate and Letrozole Combined with Low Dose Human Menopausal Gonadotropin for Controlled Ovarian Stimulation in Intrauterine Insemination Cycles

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ABSTRACT

Objective: To compare the efficacy of clomiphene citrate and letrozole in combination with low dose human menopausal gonadotropin for controlled ovarian stimulation in intrauterine insemination (IUI) cycles.

Methods: During January-2018 to December-2019 for intending 496 IUI cycles, controlled ovarian stimulation was performed with either clomiphene or letrozole combined with human menopausal gonadotropin (hMG), in two arms: subjects in one arm (Group A) were with clomiphene and hMG in 222 cycles; those in the second arm (Group B) were with letrozole and hMG in 274 cycles. Pregnancy rate and clinical pregnancy rate of both groups were considered as the primary outcomes.

Results: Patient characteristics like female age, indications for IUI, type of IUI (Artificial insemination with husband semen or donor sperm), endometrial thickness and total motile fraction (TMF) of spermatozoa of male partners were seen similar in both groups. The letrozole-hMG group (Group B) had significantly higher numbers of cycles with single dominant follicle (P=0.01) than the other one and human chorionic gonadotropin (hCG) was more frequently used as the ovulation trigger (P=0.03). Pregnancy rate (18.5% vs. 15.3%, P=0.35) and clinical pregnancy rate (18.5% vs. 15.3%, P=0.35) were similar in groups A and B, respectively.

Conclusion: Clomiphene citrate and letrozole combined with low dose human menopausal gonadotropin were equally effective for controlled ovarian stimulation in IUI cycles.

Keywords: Clomiphene; letrozole; human menopausal gonadotropin; intrauterine insemination; ovarian stimulation (Siriraj Med J 2021; 73: 198-203)

INTRODUCTION

Over the last four decades, clomiphene citrate was widely used for ovarian stimulation. Since 2001 the third generation aromatase inhibitor, letrozole become popular as its alternative agent. Several studies were performed to compare underlying functional aspects of these two drugs; two randomized trials described higher pregnancy rate with letrozole for ovulation induction in anovulatory infertility patients with polycystic ovarian syndrome (PCOS).[1,2] This was due to a better ovulation rate and

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the lack of anti-estrogenic effect on endometrium, which could be the major limiting factor of using clomiphene citrate.[3] Hence, letrozole was recommended as the first-line agent for ovulation induction in PCOS leading to anovulatory infertility.[4] Moreover, significantly higher ovulation rate with letrozole compared to clomiphene was reported in a subset of PCOS patients with clomiphene resistance.[5] Furthermore, a randomized trial of infertility patients with minimal and mild endometriosis undergoing IUI after controlled ovarian stimulation had similar pregnancy rate for both clomiphene and letrozole.[6] In a systematic review with meta-analysis of 8 randomized trials, similar pregnancy rate was seen with both letrozole and clomiphene in unexplained infertility.[7]

Clomiphene and letrozole are often used in combination with human menopausal gonadotropin (hMG) for controlled ovarian stimulation in IUI cycles. Ovarian stimulation with low dose gonadotropin is always preferred due to a low risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. Published studies using low dose gonadotropin with clomiphene or letrozole in IUI cycles show conflicting results.[8] Pregnancy rate was significantly higher with letrozole in another study.[9] In contrast, clomiphene citrate was reported as better than letrozole in terms of pregnancy rate.[10] The present study compares the efficacy of clomiphene and letrozole combined with low dose gonadotropin in overlapping regimen amidst confusing literature on the both ovarian stimulators. All categories of patients undergoing IUI including PCOS, minimal and mild endometriosis, unexplained infertility and male factor were included.

MATERIALS AND METHODS

Patient selection and controlled ovarian stimulation

The present retrospective cohort study was performed at a tertiary care infertility centre; 496 IUI cycles were performed in 2 years from January 2018 to December 2019; clomiphene or letrozole was used with human menopausal gonadotropin (hMG) for ovarian stimulation as a comparison. After routine infertility workup, fallopian tubal patency was evaluated by hysterosalpingography (HSG) or diagnostic laparoscopy with chromopertubation. IUI was advised to specific couples with unexplained infertility, ovulatory dysfunction, minimal or mild endometriosis and mild to moderate male-factor infertility. AID was advised for severely abnormal male factor, when the couple was unable to afford ART. In all cases written and informed consent was obtained from the couple.

Controlled ovarian stimulation was done with clomiphene citrate (Clofert, Svizera Healthcare, India) or letrozole (Letroz, Sun Pharma Laboratories, India) combined with urinary human menopausal gonadotropin (hMG) (GMH, Sun Pharma Laboratories, India). 'Group A' patients received clomiphene with hMG while, Group B constituted patients receiving letrozole with hMG. Clomiphene citrate 50 or 100 mg was given orally from 2nd or 3rd day of cycle for five days. Injection of human menopausal gonadotropin (75 IU) was administered intramuscularly on 5th and 7th day of cycle. Similarly letrozole 2.5 mg or 5 mg was started on 2nd or 3rd day of menstrual cycle combined with hMG (75IU) on 5th and 7th day. Follicular monitoring was conducted with transvaginal ultrasonography on 10th or 11th day of cycle. The patients were advised for further daily doses of hMG depending on the size of the dominant follicle(s). When the dominant follicle(s) reached at least 17 mm in diameter, ovulation trigger was administered and IUI was performed 38-40 hours later. Urinary human chorionic gonadotropin (hCG) 5,000 units were used as trigger for ovulation. If there were ≥ 4 follicles measuring more than 13 mm including one or two leading follicles measuring more than 16mm, injection Leuprolide acetate 1mg was administered subcutaneously as ovulation trigger to prevent ovarian hyper stimulation syndrome (OHSS). In the presence of more than 3 follicles measuring more than 16 mm, the cycle was cancelled in view of high risk for OHSS and multifetal gestation.

Semen preparation and IUI

Semen was collected by the male partner into a wide-mouth, sterile plastic container was kept at 37°C for liquefaction; semen samples were processed by using double layered density gradient method. An aliquot of 1ml 40% (v/v) density gradient medium was layered over 1 ml of 80% (v/v) density gradient medium (Nidacon International, Sweden) in a 15 ml conical polystyrene centrifuge tube (Falcon, USA). The liquefied semen sample was placed over the upper gradient layer and centrifuged at 300 g for 15 minutes. The supernatant was carefully removed without disturbing the pellet. The sperm pellet was transferred to another tube containing 3 ml of wash medium and centrifuged at 200 g for 10 minutes. The supernatant was discarded and 0.5 ml of wash medium was added to the pellet which was inseminated inside the uterine cavity using a disposable sterile IUI catheter. In AID cases, the prewashed frozen sample was thawed and inseminated.

All the patients received 200 mg of vaginal micronized progesterone twice daily for 15 days as the luteal support in the controlled ovarian stimulation cycles. The urine pregnancy test was performed 20 days post IUI. The patients with positive urine pregnancy test results were advised for trans vaginal ultrasonography after 2 weeks for confirmation of pregnancy. A clinical pregnancy was defined as the presence of gestational sac with or without fetal pole.

Sample size

A previous study reported clinical pregnancy rate of 23.3% and 13.3% with clomiphene and letrozole respectively combined with gonadotropin in IUI cycles.[10] Taking this study into consideration with α-error of 5%,power of 80% and 95% confidence interval, the sample size was calculated to be 468 with 234 in each group. Sample size calculation was done using STATA version 13. As the present study included the IUI cycles within a specific time frame and the total sample size was more than the minimum required sample, the entire available data was considered for analysis. The minimal deficiency in the sample size in the group A was due to less frequent use of clomiphene after letrozole came into clinical use.

Statistical analysis

SPSS, Inc version 20.0 (IBM, USA) was used to check the normal distribution of age, endometrial thickness and total motile fraction (TMF) in the groups by Shapiro-Wilk test. Since the dataset did not follow the normal distribution, the Mann-Whitney U test was applied to compare age, endometrial thickness and TMF between the groups. Chi-square test and Fisher's exact test were applied for categorical data to find out the difference in the number of cycles, presence of ovulation and rate of pregnancy among the groups. P value ≤0.05 was considered statistically significant. Data had statistical calculations with SPSS version 20.0.

RESULTS

Comparison of patient characteristics

Four hundred ninety six intrauterine insemination cycles were analyzed including 325 AIH (Artificial insemination with husband semen) cycles and 171 AID (Artificial insemination with donor sperm) cycles. Both the groups were compared for baseline characteristics (Table 1). Mean age of females (29.5±4.7 vs 28.9±3.7 p=0.16), cycle distribution according to different indications of IUI (p=0.11) were similar in the compared groups. There was no difference in the number of AIH (64.4% vs 66.4%) and AID (35.6% vs 33.6%) cycles (p=0.64). Mean endometrial thickness in mm (7.4±1.7 vs 7.6±1.8 p=0.41), and total motile fraction of spermatozoa in million (10.08±2.5 vs 9.9±4.4 p=0.14) were also similar. There was significant difference in number of dominant follicles (p=0.011). Letrozole-hMG group had more number of monofollicular cycles compared to clomiphene-hMG stimulated group (61.7% vs 54.5%). Conversely cycles with three dominant follicles were more in number in clomiphene-hMG group (13.1% vs 5.5%). Though human chorionic gonadotropin (hCG) was commonly used as ovulation trigger in both the groups (95.9% cycles in group A and 98.9% cycles in group B) compared to leuprolide, the difference in number of cycles assigned to different trigger agents reached statistical significance (p=0.03) (Table 2).

IUI cycle outcomes

Comparison of IUI cycle outcomes between the groups was done (Table 2). Pregnancy rate was found to be similar in group A and B (18.5% Vs 15.3% p=0.35). Similarly there was no difference in the clinical pregnancy rates for both the drugs (18.5% vs 15.3% p=0.35). There were three miscarriages in each group and Group B reported to have one twin pregnancy (Table 2).

DISCUSSION

The study groups were similar for major baseline characteristics which are likely to affect the cycle outcome. The effect of female age on IUI success rate was demonstrated in a retrospective study of frozen donor sperm cycles, where the pregnancy rate was 18.5% in women <35 years and 5.4% in women >40 years (p<0.05).[11] Similar results are obtained in the present study reflecting age having a deep impact on IUI success, especially due to oocyte quality issues. Pregnancy rate after IUI varies for different indications of IUI. In the study by Cabry-Goubet et al. clinical pregnancy rate was 17.6% for anovulation versus 8.6% in cases of endometriosis, 15% for male factor infertility and 10.7% in cases of unexplained infertility (p=0.41).[12] But, in the study by Soria et al., pregnancy rate was highest in patients with the polycystic ovarian syndrome (PCOS) and lowest in severe endometriosis (13.3% vs 6.4%. p<0.05).[13]

Association of endometrial thickness and success of IUI cycle has been demonstrated by many authors. Endometrial thickness on the day of hCG administration was significantly higher in the cycles where pregnancy was achieved.[14] But a recent systematic review and meta-analysis showed no significant impact of endometrial thickness on pregnancy rate.[15]

TABLE 1. Comparison of patient characteristics.

Parameters	Group A (n=222)	Group B (n=274)	p value
Age (Mean ±SD)	29.57±4.7	28.9±3.7	0.161*
Indication (n,%)			
Oligo anovulation	25 (11.3%)	48(17.5%)	
Unexplained	80(36.0%)	111(40.5%)	
Endometriosis	2(0.9%)	2(0.7%)	0.114‡
Male factor	98(44.1%)	94(34.3%)	
Combined	17(7.7%)	19(6.9%)	
IUI			
AIH	143 (64.4%)	182 (66.4%)	0.640†
AID	79 (35.6%)	92 (33.6%)	
No. of dominant follicles			
1	121 (54.5%)	169(61.7%)	
2	72(32.4%)	90(32.8%)	0.011†
3	29(13.1%)	15(5.5%)	
Trigger			
hCG	213(95.9%)	271(98.9%)	0.033†
Leuprolide	9(4.1%)	3(1.1%)	
Endometrial thickness	7.47±1.7	7.6±1.8	0.416*
TMF(AIH only)	10.08±2.5	9.9±4.4	0.147*

*, Mann Whitney U test was applied to compare age, endometrial thickness and TMF between group A and group B. †, Chi-square test and ‡, Fisher's exact test were applied for other categorical data. P value was significant at ≤ 0.05.

Abbreviations: n, number of subjects; SD, Standard deviation; IUI, intrauterine insemination; AIH, artificial insemination with husband's sperm; AID, artificial insemination with donor sperm; CC, clomiphene citrate; hCG, human chorionic gonadotropin; TMF, total motile fraction

TABLE 2. Comparison of IUI cycle outcomes between the groups.

Outcome (n,%)	Group A (n= 222)	Group B (n=274)	P value
Pregnancy positive	41(18.5%)	42(15.3 %)	0.352*
Clinical pregnancy	41(18.5%)	42(15.3 %)	0.352*
Multiple pregnancies	0	1	
Miscarriage	3(7.3%)	3(7.14%)	

*, Chi-square test was applied to compare the parameters between Group A and Group B. P value was significant at ≤ 0.05.

Abbreviation: n, number of subjects

Total motile fraction (TMF) of sperms in a washed semen sample is also an important parameter for IUI cycle outcome. In a study by Panda B et al. pregnancy rate was significantly lower when TMF was less than 5 million.[16]

Pregnancy rate after IUI has been positively correlated with the number of dominant follicles. But, simultaneously the risk of multiple pregnancies increases with the number of dominant follicles.[17] Soria et al. in the previously mentioned study, demonstrated higher pregnancy rate in IUI cycles with 2 or more dominant follicles than single follicle (12.3% vs 8.1%, P<0.01), where the upper limit for the number of follicles was not mentioned.[13] But in the prospective study by Kamath et al. similar pregnancy rate was documented after IUI in patients with one dominant follicle compared to patients with two and three dominant follicles (8.52% vs 13.33% vs 21.4%, P=0.303).[18] Majority of the cycles in the present study had single dominant follicle probably because of the use of low dose gonadotropin.

The choice of ovulation trigger was determined based on the number of dominant and intermediate follicles. Though many individual studies have compared pregnancy rate in IUI cycles for different types of ovulation triggers, a systematic review and meta-analysis of these studies showed no difference in pregnancy rate for hCG and GnRH agonist trigger.[19]

The present study compares efficacy of letrozole and clomiphene combined with gonadotropin in IUI cycles. Both the drugs are found to be equally effective in terms of pregnancy rate and clinical pregnancy rate. The outcome of the current study agrees with the previous studies demonstrating a similar pregnancy rate with clomiphene and letrozole in IUI cycles but differs in some aspects. In the studies by AL fozan et al and Badway et al gonadotropin was not used with clomiphene or letrozole for super ovulation.[20,21] In the study by Hembram et al[10], though gonadotropin was used along with these two drugs, only unexplained infertility cases were included. Jee et al. in a prospective study also reported similar pregnancy rate after IUI when clomiphene and letrozole were used combined with hMG.[22] The present study contradicts the only prospective study by Mitwally et al which demonstrates significantly higher pregnancy rate with letrozole combined with gonadotropin than clomiphene in unexplained infertility.[23] The above mentioned study was primarily designed to compare efficacy of clomiphene with hMG, letrozole with hMG and only hMG, where endometrial thickness was significantly higher in letrozole group that clomiphene group. In the current study, endometrial thickness was similar for both the drugs. But in patients with persistently thin endometrium, letrozole should be the drug of choice.[24] Pregnancy rate was similar with both the drugs despite a significant difference in number of dominant follicles. The maximum acceptable number of dominant follicles was three in the current study and pregnancy rate was reported not to vary with the number of dominant follicles up to three follicles.[18] Though there was difference in the type of ovulation trigger in the groups, it is unlikely to affect the pregnancy rate after IUI.[19] In majority of the cycles in the present study, letrozole or clomiphene was used with low dose hMG (75 IU). Hence it will help to choose an alternative protocol for controlled ovarian stimulation with use of low dose gonadotropin and to achieve low multiple pregnancy rates. In the current study, only one twin pregnancy was documented (1/83, 1.2%).

Retrospective nature of the study warrants caution while interpreting its outcome and applicability in clinical practice. The other limitation is unavailability of data regarding IUI cycles which was cancelled due to suboptimal and hyper response during ovarian stimulation after use of these treatment regimens. As properly randomized trials in this context are scanty in existing literatures, a well-designed randomized trial will help to reach at an appropriate conclusion while taking care of the limitations.

CONCLUSION

Clomiphene citrate and letrozole combined with gonadotropins are equally effective for controlled ovarian stimulation in IUI cycles. Either of the drugs can be used with low dose gonadotropin making ovarian stimulation more flexible depending on the availability of the drugs and physician's preference.

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Ethics: As the present study involves only retrospective analysis of pre existing data, ethical committee approval was not obtained. However, all the couples had shared informed written consent for undertaking the IUI procedure.

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Pilot Study of the Efficacy and Safety of Nail Gel Containing *Artemisia abrotanum* Extract and Glycerin in the Treatment of Nail Plate Surface Abnormality

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ABSTRACT

Objective: This study investigated the efficacy and safety of a nail gel containing glycerol and *Artemisia abrotanum* extract in treating nail plate surface abnormalities.

Methods: The nail gel was painted over the total nail surface of selected nails twice daily. All the nails were evaluated at the proximal and central parts using the Visiometer® system and according to transonychial water loss (TOWL) at baseline, and at the 2nd and 8th weeks of treatment.

Results: In total, 19 patients with a mean age of 50.6 years old were enrolled on the study, with 50 nails studied. Sixty percent of the patients showed significant clinical improvement, as determined by the total agreement between two treatment-blinded dermatologists. Regarding the visiometer system, a significant reduction in the SER value (roughness) of the nail plates was found at the 2nd week, while at the 8th week, the surface and volume values were found to be significantly decreased from baseline and also from the values at the 2nd week. There was a significant improvement in the Rku (smoothness) value at the 8th week compared to baseline. The mean TOWL at both the 2nd and 8th weeks were statistically decreased from baseline. No side effects were detected.

Conclusion: This nail gel containing glycerol and *Artemisia abrotanum* extract provided benefits in terms of improvements in the nail surface texture and water retention in patients with nail surface abnormalities.

Keywords: *Artemisia abrotanum* extract; Glycerin; nail gel; nail surface abnormality (Siriraj Med J 2021; 73: 204-208)

INTRODUCTION

The nail plate is a unit of the nail with a transparent hard and resilient character. Its shape, curvature, thickness, and surface vary depending on the location of the nail (toenail or fingernail), age, and other external factors, such as certain diseases or even the season.[1] Nail plate surface abnormalities can occur after any condition affecting the nail matrix.[2] The most common types of nail plate surface abnormalities include a pitting nail, longitudinal ridging, and transverse ridging, also called Beau's lines.[3]

Nail gel is a product used to coat the nail surface. It is frequently used to varnish nail surfaces for cosmetic aspects.[4] Aside from that, this product also assists in improving brittle nails or ingrown toenails.[5,6] A study by Nanda et al. showed the benefit of patients with nail

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plate surface abnormalities applying a nail gel to cover superficial nail plate abnormalities, such as a pitting nail, trachyonychia, and onychoschizia.[7]

The main ingredients in nail gels used in the cosmetic field are ethyl cyanoacrylate and polymethyl-methacrylate monomers, which have been reported to cause allergic contact dermatitis in some patients.[8] In therapeutic nail gels for treating nail plate surface abnormalities, these substances are typically replaced by substances with a moisturizing effect or antifungal and/or antibacterial effects.

From a review of the literature, one study reported concerns about the safety of substances extracted from *Artemisia abrotanum* leaf that are used in the spice industry and that have been added in cosmetic products.[9] However, reports about the efficacy of *Artemisia abrotanum* in treating nail plate surface abnormalities in Asian populations are limited. Consequently, this study aimed to investigate the efficacy of *Artemisia abrotanum* extract using subjective and objective measurements as well as the safety of nail gel containing glycerol (a natural moisturizing factor and moisturizer)[10-14] and *Artemisia abrotanum* extract (essential oils with antifungal and/or antibacterial effects)[15-17] in treating nail plate surface abnormalities.

MATERIALS AND METHODS

This prospective study was conducted at Siriraj Hospital, Mahidol University, Thailand. The protocol was approved by the Siriraj Institutional Review Board (Si 372/2015) and registered with ClinicalTrials.gov (No. NCT02582762). In total, 20 patients with abnormalities of the nail plate surface of one or more nails that had persisted for more than 3 months, and who were aged at least 18 years old, were enrolled and asked to complete informed consent. The exclusion criteria were patients who had an allergy to any of the product ingredients, a severe medical condition, nail infection, pregnancy, lactation, or a history of manicure or nail polish application within the previous 1 month, or a history of biotin or zinc supplementation within the previous 3 months. The patient's demographic data and the abnormal characteristics of their nail surfaces were recorded. The number of selected nails per person varied from 1–3 nails. The patients were instructed to apply over-the-counter (OTC) nail gel products that consisted of aqua, glycerol, dimethicone, PEG-40 hydrogenated castor oil, 1,5-pentanediol, propylene glycol, carbomer, sodium hydroxide, and *Artemisia abrotanum* extract, and that had been approved by the Thai Food and Drug Administration, twice daily on the nail with the surface abnormalities. The nail gel was painted over the total area of the nail surface as a single layer by swiping the brush in a straight line from the proximal part of the nail to the distal part. All the selected nails were evaluated at the proximal and central parts of the nail using the Visiometer® system (Courage + Khazaka Electronic GmbH, Cologne, Germany) and according to transonychial water loss (TOWL) using the Tewameter® TM 300 system (Courage + Khazaka Electronic GmbH, Cologne, Germany) at baseline, and at 2 weeks and 8 weeks after treatment. We did not evaluate the distal part of the nail because this could be disturbed by external causes, such as trauma to the nail. Patients were asked to rate their satisfaction with the nail improvement by completing a 6-item questionnaire covering aspects such as visible nail improvement and quality of life, scoring each question from 0 to 5 (0 = very dissatisfied, 1 = dissatisfied, 2 = somewhat dissatisfied, 3 = somewhat satisfied, 4 = satisfied, 5 = very satisfied) at 2 weeks and 8 weeks after initiating treatment. Two-blinded dermatologists assessed random photographs of the nails taken with the Visiometer® and interpreted the results as: no improvement, improved, or worsened.

Descriptive statistics were used to describe the demographic data. Associations between categorical variables were analyzed by Chi-square test or Fisher's exact test. Continuous variables were analyzed by Student's t-test or Mann-Whitney U test. Repeated measures ANOVA was used to evaluate the changes in the nail plate surface abnormalities. The Wilcoxon signed-rank test was used to evaluate the changes in the questionnaire scores. The kappa statistic was used to evaluate the inter-observer reliability between the two blinded dermatologists. A p-value ≤ 0.05 was considered statistically significant. All the statistical analyses were performed using SPSS for Windows version 18.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

In total, 20 patients were initially enrolled in the study, but one was excluded because follow-up proved too difficult. Thus, a total of 19 healthy patients, comprising 15 women and 4 men, with a mean age (standard deviation [SD]) of 50.6 (11.5) years old, were included in the analysis. The mean (SD) frequency of hand washing was 8.8 (2) times per day. The characteristics of the surfaces of the 50 nails tested in the study are shown in Table 1.

Physicians' assessments

From photographs taken by the Visiometer® comparing the tested nails at baseline and at the 8th week after treatment, 60% of the nails showed a significant improvement, as observed by the two blinded dermatologists (Figs 1 and 2).

TABLE 1. Nail characteristics of all the patients.

Nail characteristics	N (%)
Linear	39 (78)
Transverse groove	1 (2)
Transverse ridging	5 (10)
Longitudinal groove	0
Longitudinal ridging	33 (66)
Onychoschizia	0
Pits	17 (34)
Trachyonychia	0
Pitting nail	17 (34)
Scale	0
Others	2 (4)
Brittle nail	2 (4)

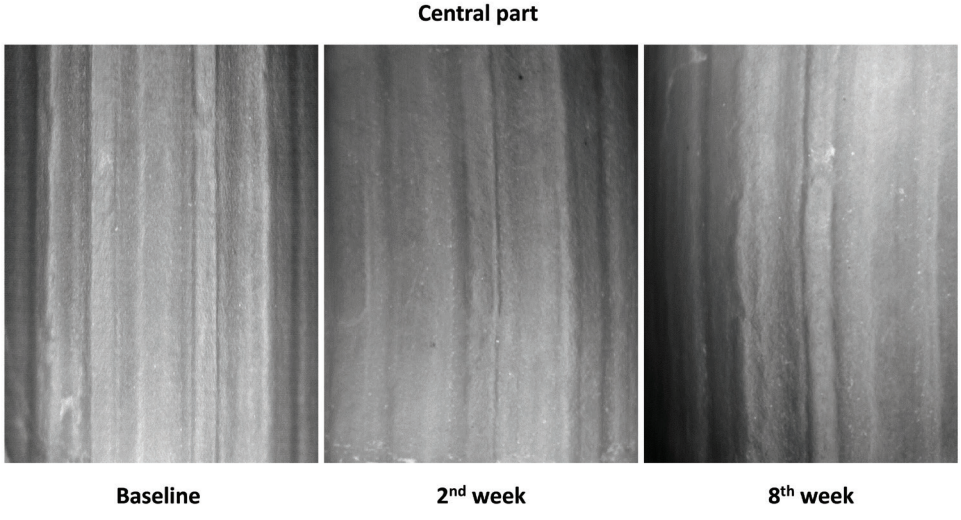

Fig 1. The nail surface at the central part at baseline, and at the 2nd week and 8th week

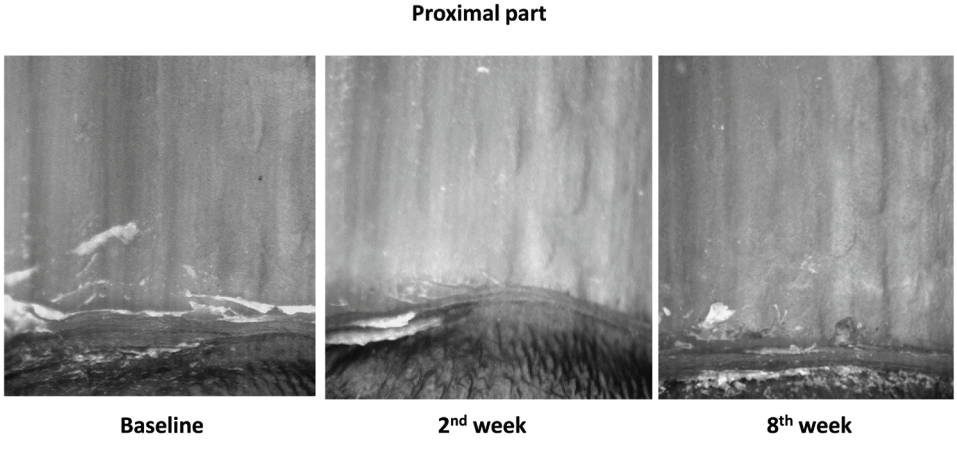

Fig 2. The nail surface at the proximal part at baseline, and at the 2nd week and 8th week

The inter-observer reliability between the two blinded dermatologists was consistent (K = 0.855, p < 0.001). No side effects were observed.

Patients' assessments

According to the patients' satisfaction levels of their nail plate improvement, there was a significant increase in the total satisfaction scores at the 8th week (24.8 ± 3.8) compared to at the 2nd week (20.7 ± 3.6) with p < 0.001.

Bioengineering assessment

Regarding the visiometer system, a significant reduction in the SER (roughness) value was found at the 2nd week for the central part of the nail (p = 0.025; Fig 3a). At the 8th week, the surface value was significantly decreased from both baseline and from the 2nd week in the central area (p < 0.001 and p < 0.001; respectively; Fig 3b), while the smoothness value (Rku) was significantly decreased from baseline and from the 2nd week in the proximal and central areas (p = 0.028 and p = 0.027; respectively; Fig 3c). There was a significant improvement in the surface smoothness at the 8th week compared to baseline (p = 0.044). Regarding the TOWL values, the mean TOWL values at the 2nd week and 8th week were both statistically decreased from baseline (p < 0.001 and p < 0.001; respectively; Fig 3d).

DISCUSSION

This study demonstrated the efficacy of nail gel containing glycerol and *Artemisia abrotanum* leaf extract for improving the nail surface texture and water retention in patients with nail plate surface abnormalities, especially those with pitted or linear lesions. The improvement was found to be noticeable at 2 weeks after the initial application and could be maintained for up to 2 months without any side effects. In addition, this nail gel was also found to be satisfactory by the patients in terms of the treatment's overall aspects (clinical outcomes and application).

In terms of the nail rehydration effect, the high potential of glycerol for restoring stratum corneum hydration and assisting the skin barrier function is well known,[10-14] and this concorded with the significant decline in the TOWL values found in our study. Although the mechanism remains unknown, one theory is that glycerol may be absorbed, leading to the formation of complex glycerolipid-like compounds.[11]

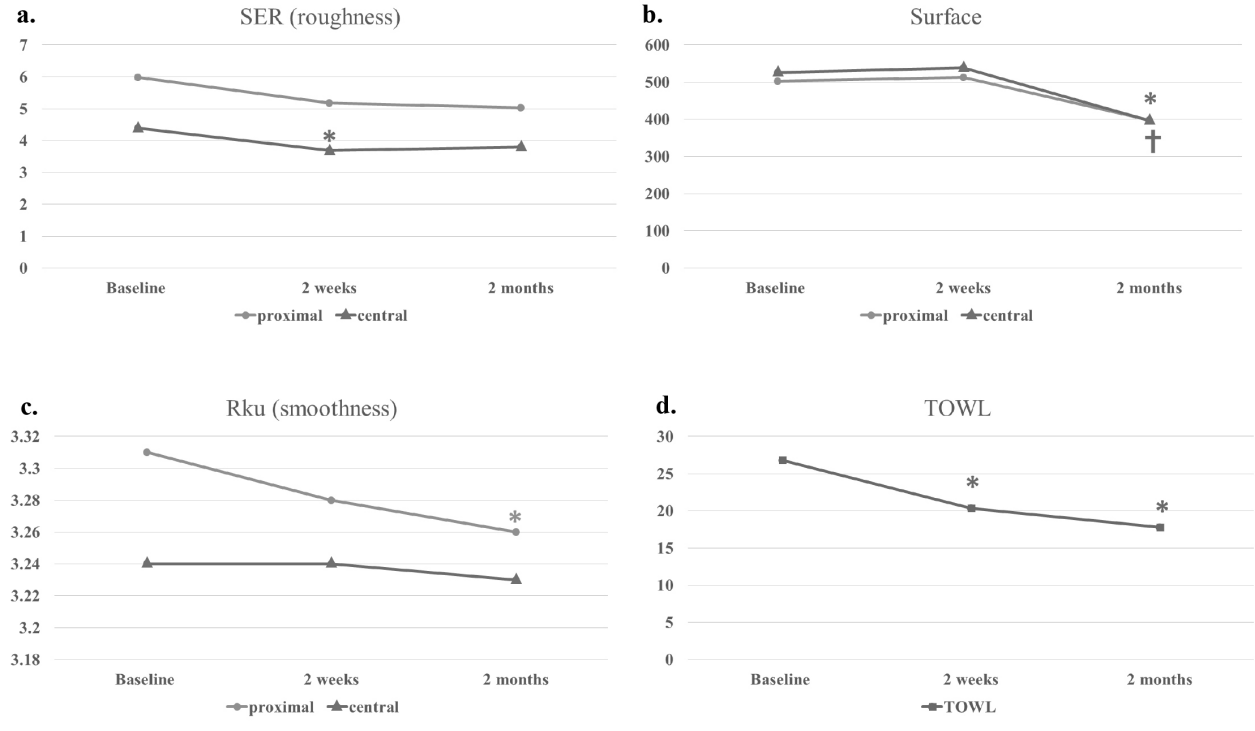

Fig 3. Bioengineering assessments using the Visiometer® and Tewameter® systems at baseline, and at the 2nd and 8th weeks of treatment: (a) SER values, (b) Surface values, (c) Rku values, and (d) TOWL values.

*Significant difference from baseline. †Significant difference from the 2nd week.

Abbreviations: SER, roughness; Rku, smoothness; TOWL, transonychial water loss

Artemisia abrotanum leaf extract is a volatile oil containing 1, 8-cineole, linalool, davanone, thujyl alcohols; favonols; tannins, cafeic acid; and coumarins.[18] Several studies have reported the usefulness of the various properties of *Artemisia abrotanum* leaf extract, including for prophylactic and therapeutic management in allergic rhinitis and its antimicrobial effect against *Malassezia* spp., *Candida albicans*, and *Staphylococcus aureus*.[15-17] However, the mechanism of how it assists stratum corneum hydration and how it can improve the nail surface need to be further elucidated.

There are several limitations in this study to note. This study was a pilot study with a limited sample size and a predominantly female population. Further study with a larger and more mixed population is required. Since this study period was 2 months in total, prolonged follow-up to demonstrate the long-term efficacy of the nail gel treatment remains to be investigated.

In conclusion, the efficacy and safety of nail gel containing glycerol and *Artemisia abrotanum* leaf extract were investigated for the first time. It was found that the gel provided benefits in improving the nail surface texture and water retention in patients with nail surface abnormalities. However, further studies are required to describe the mechanism of action and to confirm its long-term efficacy and safety.

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Conflict of interest: None declared

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Living Well with Kidney Disease by Patient and Care-Partner Empowerment: Kidney Health for Everyone Everywhere

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ABSTRACT

Living with chronic kidney disease (CKD) is associated with hardships for patients and their care-partners. Empowering patients and their care-partners, including family members or friends involved in their care, may help minimize the burden and consequences of CKD related symptoms to enable life participation. There is a need to broaden the focus on living well with kidney disease and re-engagement in life, including an emphasis on patients being in control. The World Kidney Day (WKD) Joint Steering Committee has declared 2021 the year of "Living Well with Kidney Disease" in an effort to increase education and awareness on the important goal of patient empowerment and life participation. This calls for the development and implementation of validated patient-reported outcome measures to assess and address areas of life participation in routine care. It could be supported by regulatory agencies as a metric for quality care or to support labelling claims for medicines and devices. Funding agencies could establish targeted calls for research that address the priorities of patients. Patients with kidney disease and their care-partners should feel supported to live well through concerted efforts by kidney care communities including during pandemics. In the overall wellness program for kidney disease patients, the need for prevention should be reiterated. Early detection with a prolonged course of wellness despite kidney disease, after effective secondary and tertiary prevention programs, should be promoted. WKD 2021 continues to call for increased awareness of the importance of preventive measures throughout populations, professionals, and policy makers, applicable to both developed and developing countries.

Keywords: Patient empowerment; care-partner; low-middle-income countries; health policy (Siriraj Med J 2021; 73: 209-215)

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Patient priorities for living well: a focus on life participation

CKD, its associated symptoms, and its treatment, including medications, dietary and fluid restrictions, and kidney replacement therapy can disrupt and constrain daily living, and impair the overall quality of life of patients and their family members. Consequently, this can also impact treatment satisfaction and clinical outcomes.[1] Despite this, the past several decades have seen limited improvement in the quality of life of people with CKD.[1] To advance research, practice, and policy, there is increasing recognition of the need to identify and address patient priorities, values, and goals.[1]

Several regional and global kidney health projects have addressed these important questions including the *Standardised Outcomes in Nephrology* (SONG) with more than 9,000 patients, family members, and health professionals from over 70 countries.[2,3] Across all treatment stages, including CKD, dialysis and transplantation, SONG participating children and adults with CKD consistently gave higher priority to symptoms and life impacts than health professionals.[2,3] In comparison, health professionals gave higher priority to mortality and hospitalization than patients and family members. The patient-prioritized outcomes are shown in Fig 1. Irrespective of the type of kidney disease or treatment stage, patients wanted to be able to live well, maintain their role and social functioning, protect some semblance of normality, and have a sense of control over their health and wellbeing.

Life participation, defined as the ability to do meaningful activities of life including, but not limited to, work, study, family responsibilities, travel, sport, social, and recreational activities, was established a critically important outcome across all treatment stages of CKD.[1,2] The quotations from patients with kidney disease provided in Appendix 1 demonstrates how life participation reflects the ability to live well with CKD.[4] According to the World Health Organization (WHO), participation refers to "involvement in a life situation."[5] This concept is more specific than the broader construct of quality of life. Life participation places the life priorities and values of those affected by CKD and their family at the center of decision making. The World Kidney Day Steering Committee calls for the inclusion of life participation, a key focus in the care of patients with CKD, to achieve the ultimate goal of living well with kidney disease. This calls for the development and implementation of validated patient-reported outcome measures, that could be used to assess and address areas of life participation in routine care. Monitoring of life participation could be supported by regulatory agencies as a metric for quality care or to support labelling claims for medicines and devices. Funding agencies could establish targeted calls for research that address the priorities of patients, including life participation.

Patient empowerment, partnership and a paradigm shift towards a strengths-based approach to care

Patients with CKD and their family members including care-partners should be empowered to achieve the health outcomes and life goals that are meaningful and important to them. The WHO defines patient empowerment as "a process through which people gain greater control over decisions or actions affecting their health,"[6] which requires patients to understand their role, to have knowledge to be able to engage with clinicians in shared decision-making, skills, and support for self-management. For patients receiving dialysis, understanding the rationale for a lifestyle change, having access to practical assistance and family support promoted patient empowerment, while feeling limited in life participation undermined their sense of empowerment.[7]

The World Kidney Day Steering Committee advocates for strengthened partnership with patients in the development, implementation, and evaluation of interventions for practice and policy settings, that enable patients to live well with kidney diseases. This needs to be supported by consistent, accessible, and meaningful communication. Meaningful involvement of patients and family members across the entire research process, from priority setting and planning the study through to dissemination and implementation, is now widely advocated.[8] There have also been efforts, such as the *Kidney Health Initiative*, to involve patients in the development of drugs and devices to foster innovation.[9] We urge for greater emphasis on a strengths-based approach as outlined in Table 1, which encompasses strategies to support patient resilience, harness social connections, build patient awareness and knowledge, facilitate access to support, and establish confidence and control in self-management. The strengths-based approach is in contrast to the medical model where chronic disease is traditionally focussed on pathology, problems, and failures.[10] Instead, the strengths-based approach acknowledges that each individual has strengths and abilities to overcome the problems and challenges faced, and requires collaboration and cultivation of the patient's hopes, aspirations, interests, and values. Efforts are needed to ensure that structural biases, discrimination, and disparities in the health care system also need to be identified, so all patients are given the opportunity to have a voice.

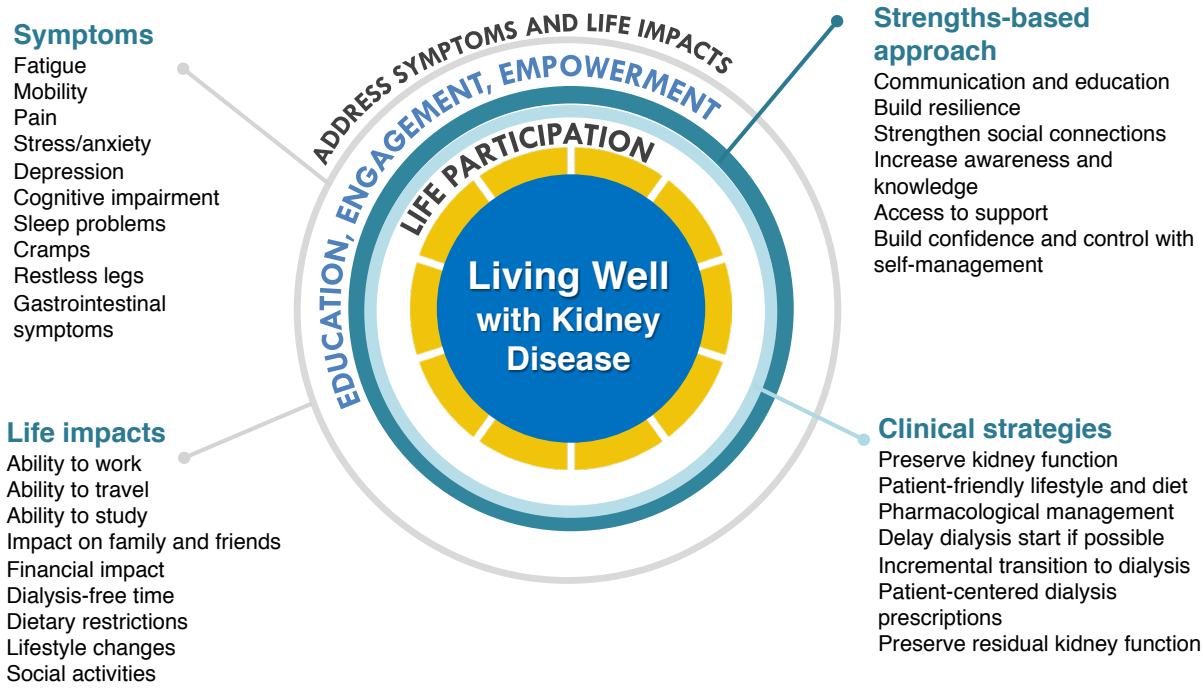

Fig 1. Conceptual framework of "Living Well with Kidney Disease" based on patient centeredness and empowering patient with focus on effective symptom management and life participation.

Appendix 1. Quotations from patients with CKD related to priorities for living well.

"I don't want to think about dying from my disease. I want to be able to live well with my disease." – Patient with CKD
"Life participation is most important because without it, you can't do anything." – Child with CKD
"Maybe it's as simple as asking patients whether, how well they are able to participate in the life that they want to lead because it's going to be different for different people" – Kidney transplant recipient
"Everyone has to face death, what I would like to have is a good quality of life rather than to face death." – Kidney transplant recipient
"So, it doesn't actually really matter what the numbers say, and some of my numbers should have suggested that I should be feeling a lot worse than what I actually was, it's about how much I feel I can do and participate in my life and feel normal." – Patient with CKD
"I'm still living. I get out of bed, and I'm still living and still breathing. As long as I can do that, I'm going to carry on and be positive because life is short." Patient with CKD[4]
"I put life participation because I know that looking from the outside, I know [his kidney disease] stops [him] from thinking bigger. . .Although that's really big, there's this life that has to happen at the same time." – Family member
"Amazed at comments from professional(sic) about travel, free time, etc they seem to think the mechanics of dialysis far more important. Dialysis is a treatment which keeps us alive to live a life, not just to wait for death. – Patient receiving dialysis
"I prefer to be above ground, then below ground. So why not enjoy life whilst being above ground." Adam Martin
"Over the years, I have learned to worry less, control my emotions, and not fear death. I keep my mind active. I follow the advice of the philosopher-emperor Marcus Aurelius to 'love the hand that fate (has dealt me) and play it as (my) own'. Living well with CKD means to live the best life I can in the time I have available….Living well with CKD is the same as living well." – Tess Harris
"While CKD brings me some limitations, I can maximize the possibility to live well. I kept working when I was doing hemodialysis. After transplant, I could live: study, work, travel, marry, have children, and service the community." – Maggie Ng

*Personal communication; quotations are identified by name with permission

TABLE 1. Suggested strategies for "living well with CKD" using a strengths-based approach.

Strengths-based approach	Suggested strategies
Build resilience	• Identify or provide strategies and resources to manage stress and functioning when encountering challenges, adversity and trauma (e.g. commencement of dialysis)
Harness social connections	• Facilitate connections with other patients to learn coping strategies and for support • Support family members/caregivers
Build awareness and knowledge	• Provide education (including practical advice) on diet and lifestyle modifications • Understand, identify, and address the potential impacts of CKD (e.g. cognitive function). • Encourage patients to ask questions. • Encourage the use of knowledge to empower and prepare for the future.
Facilitate access to support	• Refer to allied health care professionals (e.g. dietitian, social worker, mental health professionals, occupation therapists) • Provide support that enables the patient to participate in important life activities e.g. work.
Establish confidence and control in self-management	• Support informed and shared decision-making (including dialysis, kidney transplantation, conservative or non-dialytic care) • Encourage patients to learn to "get in tune" with what works well for them and to voice any concerns, and work together to develop better management strategies to enable patients to feel better. • Provide strategies to prevent or manage complications (e.g. infection) • Support open communication regarding goals, concerns, and priorities

Abbreviations: CKD: chronic kidney disease (not receiving kidney replacement therapy), HD: hemodialysis, PD: peritoneal dialysis, Tx: transplant, RKF: Residual kidney function

The role of care-partner

A care-partner is often an informal caregiver who is also a family member of the patient with CKD.[11] They may take on a wide range of responsibilities including coordinating care (including transportation to appointments), administration of treatment including medications, home dialysis assistance, and supporting dietary management. Caregivers of patients with CKD have reported depression, fatigue, isolation, and also burden out. The role of the care-partner has increasingly become more important in CKD care given the heightened complexity in communicative and therapeutic options including the expansion of telemedicine under the COVID-19 pandemic and given the goal to achieve higher life expectancy with CKD.[12] The experience of caring for a partially incapacitated family member with progressive CKD can represent a substantial burden on the care-partner and may impact family dynamics. Not infrequently, the career goals and other occupational and leisure aspects of the life of the care-partner are affected because of CKD care partnership, leading to care-partner overload and burnout. Hence, the above-mentioned principles of life participation need to equally apply to care-partners as well as all family members and friends involved in CKD care.

Living with kidney disease in low-income regions

In low and lower-middle-income countries (LICs and LMICs) including in sub-Saharan Africa, South East Asia, and Latin America, patient's ability to self-manage or cope with the chronic disease vary but may often be influenced by internal factors including spirituality, belief

system, and religiosity, and external factors including appropriate knowledge of the disease, poverty, family support system, and one's grit and social relations network. The support system comprising healthcare providers and caregivers plays a crucial role as most patients rely on them in making decisions, and for the necessary adjustments in their health behavior.[13] In LIC regions, where there are often a relatively low number of physicians and even lower number of kidney care providers per population especially in rural areas, a stepwise approach can involve local and national stakeholders including both non-governmental organizations and government agencies by 1) extending kidney patient education in rural areas, 2) adapting telehealth technologies if feasible to educate patients and train local community kidney care providers and 3) implementing effective retention strategies for rural kidney health providers including adapting career plans and competitive incentives.

Many patients in low resource settings present in very late stage needing to commence emergency dialysis.[14] The very few fortunate ones to receive kidney transplantation may acquire an indescribable chance to normal life again, notwithstanding the high costs of immunosuppressive medications in some countries. For some patients and care-partners in low-income regions, spirituality and religiosity may engender hope, when ill they are energized by the anticipation of restored health and spiritual wellbeing. For many patients, informing them of a diagnosis of kidney disease is a harrowing experience both for the patient (and caregivers) and the healthcare professional. Most patients present to kidney physicians (usually known as "renal physicians" in many of these countries) with trepidations and apprehension. It is rewarding therefore to see the patient's anxiety dissipate after reassuring him or her of a diagnosis of simple kidney cysts, urinary tract infection, simple kidney stones, solitary kidneys, etc., that would not require extreme measures like kidney replacement therapy. Patients diagnosed with glomerulonephritis who have an appropriate characterization of their disease from kidney biopsies and histology; who receive appropriate therapies and achieve remission are relieved and are very grateful. Patients are glad to discontinue dialysis following resolution of AKI or acute on CKD.

Many CKD patients who have residual kidney function appreciate being maintained in a relatively healthy state with conservative measures, without dialysis. They experience renewed energy when their anemia is promptly corrected using erythropoiesis-stimulating agents. They are happy when their peripheral oedema resolves with treatment. For those on maintenance hemodialysis who had woeful stories from emergency femoral cannulations, they appreciate the construction of good temporary or permanent vascular accesses. Many patients in low resource settings present in very late stage needing to commence emergency dialysis. Patients remain grateful for waking from a uremic coma or recovering from recurrent seizures when they commence dialysis.

World kidney day 2021 advocacy

World Kidney Day 2021 theme on 'Living Well with Kidney Disease' is deliberately chosen to have the goals to redirect more focus on plans and actions towards achieving patient-centred wellness. "Kidney Health for Everyone, Everywhere" with emphasis on patient-centred wellness should be a policy imperative that can be successfully achieved if policy makers, nephrologists, health care professionals, patients, and care partners place this within the context of comprehensive care. The requirement of patient engagement is needed. World Health Organization (WHO) in 2016 put out an important document on patient empowerment (WHO 2016): 'Patient engagement is increasingly recognized as an integral part of health care and a critical component of safe people-centred services. Engaged patients are better able to make informed decisions about their care options. In addition, resources may be better used if they are aligned with patients' priorities and this is critical for the sustainability of health systems worldwide. Patient engagement may also promote mutual accountability and understanding between patients and health care providers. Informed patients are more likely to feel confident to report both positive and negative experiences and have increased concordance with mutually agreed care management plans. This not only improves health outcomes but also advances learning and improvement while reducing adverse events.' In the ISN Community Film Event at World Congress of Nephrology (WCN) 20 (ISN Community Film Event 2020), it is good to see a quote in the film from patients: "Tell me. I will forget; Show me. I will remember; Involve me. I will understand." ISN Global Kidney Policy Forum 2019 included a patient speaker Nicki Scholes-Robertson from New Zealand: 'Culturally appropriate and sensitive patient information and care are being undertaken in New Zealand to fight inequities in kidney health, especially in Maori and other disadvantaged communities.'

World Kidney Day 2021 would like to promote to the policy makers on increasing focus and resources on both drug and non-drug programmes in improving patient wellness. Examples include funding for erythropoiesis-stimulating agents and anti-pruritic agents for managing

anemia and itchiness respectively, just name but a few.[15,16] Home dialysis therapies have been consistently found to improve patient autonomy and flexibility, quality of life in a cost-effective manner, enhancing life participation. Promoting home dialysis therapies should tie in with appropriate 'assisted dialysis' programs to reduce patient and care partner fatigue and burnout. Also, examples like self-management programmes, cognitive behavioural therapy, and group therapies for managing depression, anxiety, and insomnia should be promoted before resorting to medications.[17] The principle of equity recognizes that different people with different levels of disadvantage require different approaches and resources to achieve equitable health outcomes. The kidney community should push for adapted care guidelines for vulnerable and disadvantaged populations. The involvement of primary care and general physicians especially in LICs and LMICs would be useful in improving the affordability and access to services through the public sector in helping the symptom management of CKD patients and improve their wellness. In the overall wellness program for kidney disease patients, the need for prevention should be reiterated. Early detection with a prolonged course of wellness despite kidney disease, after an effective secondary prevention program, should be promoted.[18] Prevention of CKD progression can be attempted by lifestyle and diet modifications such as a plant-dominant low protein diet and by means of effective pharmacotherapy including administration of sodium-glucose transport protein 2 (SGLT2) inhibitors.[19] WKD 2021 continues to call for increased awareness of the importance of preventive measures throughout populations, professionals, and policy makers, applicable to both developed and developing countries.[18]

CONCLUSION

Effective strategies to empower patients and their care-partners strive to pursue the overarching goal of minimizing the burden of CKD related symptoms in order to enhance patient satisfaction, health-related quality of life, and life participation. World Kidney Day 2021 theme on 'Living Well with Kidney Disease" is deliberately chosen to have the goals to redirect more focus on plans and actions towards achieving patient-centered wellness. Notwithstanding the COVID-19 pandemic that had overshadowed many activities in 2020 and beyond, the World Kidney Day Steering Committee has declared 2021 the year of "Living well with Kidney Disease" in an effort to increase education and awareness on the important goal of effective symptom management and patient empowerment. Whereas the World Kidney Day continues to emphasize the importance of effective measures to prevent kidney disease and its progression,[18] patients with preexisting kidney disease and their care-partners should feel supported to live well through concerted efforts by kidney care communities and other stakeholders throughout the world even during a world-shattering pandemic as COVID-19 that may drain many resources.[20] Living well with kidney disease is an uncompromisable goal of all kidney foundations, patient groups, and professional societies alike, to which the International Society of Nephrology and the International Federation of Kidney Foundation World Kidney Alliance are committed at all times.

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