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International Journal *of* Integrated Health Sciences

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Venous Thromboembolism Prophylaxis and The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) Score in Medical Illness Patients

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Abstract

Objective: To describe applicability of The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) score to implement venous thromboembolism prophylaxis in patients with medical illness in Hasan Sadikin General Hospital Bandung.

Methods: This study was descriptive, cross-sectional research from database was performed on December 2018. Inclusion criteria in this study were all patients hospitalized in Department of Internal Medicine, Hasan Sadikin General Hospital in November 2018 with medical illness, which is patients with medical condition involves a more systemic, pharmaceutical approach to treatment. Exclusion criteria were surgical disease, which is requires some form of intervention such as surgery, also patients with incomplete medical record were excluded.

Results: There were 162 patients (56% male and 44% female). Median age were higher in males compared to females (53 [18–76] vs. 49 [18–85]) years. Low-risk (score <2), medium-risk (score 2 – 3), and high-risk (score >4) for IMPROVE venous thromboembolism score were 77.2%, 17.3%, and 5.6% respectively.). Low-risk (score <7) and high-risk (score >7) for IMPROVE bleeding score were 75.9% and 24.1% respectively. Medical thromboprophylaxis were given to 14.8% patients, with 91.7% and 8.3% of the patients received unfractionated heparin (UFH) and low-molecular weight heparin (LMWH) respectively. Thromboprophylaxis was given in 88.9% of high-risk patients for venous thromboembolism. There were 18.7% patients with low-risk and 2.6% with high-risk for bleeding that received prophylaxis.

Conclusion: The majority of inpatients treated with thromboprophylaxis had low-risk for both thromboembolism and bleeding. The rate of thromboprophylaxis usage was still low; with the most frequently used thromboprophylaxis agent was UFH. Most of high-risk patients for venous thromboembolism received thromboprophylaxis.

Keywords: Bleeding risk, IMPROVE score, thromboembolism risk, thromboprophylaxis

Introduction

Venous thromboembolism is characterized with venous thrombosis, frequently occurring in the lower extremities. Several cases of venous thrombosis may cause embolization, particularly to lungs. The emboli may cause partial or complete obstruction of pulmonary arteries or its branches.[1]

Predisposing factors of venous thrombosis may be defined using Virchow triad, consisting of: stasis of blood flow, hypercoagulability, and endothelial injury. Stasis of blood flow may be caused by several conditions, such as immobilization, bed rest, congestive heart failure, and previous history of venous

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thrombosis. Hypercoagulability may be found in patients with history of malignancy, anticardiolipin antibody, nephrotic syndrome, essential thrombocytosis, estrogen therapy, heparin usage (heparin-induced thrombocytopenia), inflammatory bowel disease, paroxysmal nocturnal hemoglobinuria, disseminated intravascular coagulation, and deficiency of several proteins (such as protein C, protein S, and antithrombin III). Endothelial injury may occur due to trauma or internal bleeding.[2]

Annual incidence of venous thromboembolism in Europe and United States were approximately 50/100,000 persons per year. Genetic variability may be noted, with lower incidence were found in Asian and Hispanic population compared to Caucasians, African Americans, Latino, and Asia-Pacific populations. No significant incidence between both sexes were noted. Increasing trend in incidence of lung emboli were noted, with annual incidence rate of lung emboli of 1 in 1000 persons in United States. Pulmonary emboli occurs in 60–80% cases of venous thromboembolism, 50% of which cases were asymptomatic. Lung emboli is one of the most frequent cause of death, ranking 3rd and casing about 650,000 mortalities each year.[3-6]

Approximately 100,000 and 300,000 deaths related to venous thromboembolism were reported annually in United States and Europe, respectively. Venous thromboembolism related mortalities may be prevented by using thromboprophylaxis medications. No consensus regarding the dosage of the medication has been reached, due to the risk of bleeding as a possible side effect of thromboprophylaxis medications.[7] The IMPROVE (International Medical Prevention

Registry on Venous Thromboembolism) predictive score was designed to assesses the risk of VTE in hospitalized medical patients. IMPROVE scores may be utilized to assess the risk of thromboembolism and bleeding.[8] This study aims to assess the risk factors associated with venous thromboembolism and bleeding according to IMPROVE scores and administration of thromboprophylaxis medications of inpatients with medical illness in Department of Internal Medicine , Hasan Sadikin General Hospital.

Methods

The descriptive, cross-sectional study was performed on December 2018. Data were collected from database of inpatients hospitalized with medical illness in Department of Internal Medicine Dr. Hasan Sadikin General Hospital Bandung. Inclusion criteria in this study were all patients hospitalized in November 2018 with medical illness, which is patients with medical condition involves a more systemic, pharmaceutical approach to treatment. Exclusion criteria were surgical disease, which is requires some form of intervention such as surgery, also patients with incompleted medical record were excluded. Several variables included in this study are as described below.

Risk for venous thromboembolism,

Table 1 IMPROVE score for Thromboembolism[8]

Parameter	Score
History of thromboembolism	3
Thrombophilia	2
Paralysis of lower extremities	2
Malignancy	2
Immobilization ≥7 days	1
History of admittance to intensive care unit	1
Age >60 years	1

Table 2 IMPROVE Score for Bleeding[8]

Parameter	Score
Previous history of gastroduodenal ulcer	4.5
History of bleeding (last 3 months)	4
Platelet count <50x10^9 /L	4
Previous history of hepatic failure (INR>1.5)	2.5
History of admittance to intensive care unit	2.5
History of central venous catheter insertion	2
Rheumatic diseases	2
History of malignancy	2
Male sex	1
Age 40–84 vs ≥ 85 years	1.5 vs 3.5
Glomerular filtration rate 30-59 vs <30	1 vs 2.5

categorized according to IMPROVE score: low risk (score <2), moderate risk (score 2–3), and high risk (score ≥4) (Table1).

Risk for bleeding, categorized according to IMPROVE score: low risk (score <7) and high risk (score ≥7) (Table 2).

Thromboprophylaxis refers to administration of anticoagulants, specifically unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) during the period of hospitalization.

Descriptive statistics were used in presenting the results. Median, mean, and percentage were used as descriptive statistics in describing the patients with risk of venous thromboembolism and bleeding.

Table 3 Subjects Characteristics

Characteristics	Total (n=162)
Sex, n (%)	
Male	91 (56)
Female	71 (44)
Age (years)	
Median (range)	51 (18–85)
VTE risk, n (%)	
Low risk	125 (77,2)
Moderate risk	28 (17,3)
High risk	9 (5,5)
Bleeding risk, n (%)	
Low risk	123 (75,9)
High risk	39 (24,1)
Thromboprophylaxis, n (%)	
UFH	22 (13,6)
LMWH	2 (1,2)
No thromboprophylaxis	138 (85,2)
VTE risk with thromboprophylaxis, n (%)	
Low risk	0 (0)
Moderate risk	16 (57,1)
High risk	8 (88,9)
Bleeding risk with thromboprophylaxis, n (%)	
Low risk	23 (18,7)
High risk	1 (2.6)

Results

Total participants from database who fulfilled inclusion were 162 patients, with distribution of 56% males and 44% females. Male patients were older compared to female patients (Median 53 [18–76] vs 49 [18–85]) years. Risk of thromboembolism was assessed using IMPROVE score: 77.2% low risk patients (scores <2); 17.3% moderate risk patients (score 2–3); and 5.6% high risk patients (scores ≥4). Risk of bleeding was assessed using IMPROVE score: 75.9% low risk patients (scores <7) and 24.1% high risk patients (scores ≥7). Thromboprophylaxis medications were given to 14.8% of the patients included in the study. The medications given were unfractionated heparin (UFH) in 91.7% patients and low-molecular weight heparin (LMWH) in 8.3% patients.

Patients with low risk for venous thromboembolism did not receive thromboprophylaxis. There were 57.1% medium risk and 88.9% of high risk patients for venous thromboembolism that received thromboprophylaxis medications. There were 17.8% low risk and 2.6% medium risk patients for bleeding that received thromboprophylaxis medications. Subject's characteristics were described in Table 3.

From 37 patients with venous thromboembolism, the majority of these patients had previous history of malignancy. There were 27 (73%) patients with previous history of malignancy and 10 (27%) patients with previous history of prolonged immobilization. The majority of the patients with previous history of malignancy had received thromboprophylaxis: 22 (81.5%) patients received thromboprophylaxis and 5 (18.5%) patients did not receive thromboprophylaxis. On subjects with previous history of prolonged immobilization, 2 (20%) patients had received thromboprophylaxis and 8 (80%) patients did not receive thromboprophylaxis.

There were 3 high risk patients for bleeding: 2 (66.7%) of the patients had not received thromboprophylaxis and 1 (33.3%) patient had received thromboprophylaxis. The patient that was given thromboprophylaxis had previous history of malignancy.

Discussion

International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) score was formulated in order to assess the risk of venous thromboembolism and bleeding. The

score had listed 7 risk factors in assessing the risk of venous thromboembolism: previous history of venous thromboembolism; thrombophilia; paralysis of lower extremities; previous history of malignancy; prolonged immobilization ($\geq$7 days); and previous history of admittance in intensive care unit (in patients aged >60 years). There are three risk stratifications in thromboembolism risk: low risk (score <2), moderate risk (score 2–3), and high risk (score $\geq$4). Assessment of risk for bleeding utilize 13 risk factors to be examined on the patient: previous history of gastroduodenal ulcers; previous history of bleeding in the last 3 months; platelet count <50x10^9/L; previous history of hepatic failure; previous history of admittance in intensive care unit ; previous history of central venous catheter insertion; previous history of rheumatic diseases; previous history of malignancy; age; sex; and glomerular filtration rate. The risk is further stratified into low risk (score <7) and high risk (score $\geq$7). Patients with moderate risk for thromboembolism (score >2) and low risk for bleeding (score <7) are recommended to be given thromboprophylaxis medication in order to prevent emboli formation. In patients with high risk of bleeding (score $\geq$7), mechanical thromboprophylaxis is recommended in order to reduce the risk of emboli formation.[9]

IMPROVE scoring system has been routinely utilized in 12 countries: Australia, Brazil, Canada, Colombia, France, Germany, Italy, Japan, Spain, England, United States, and Venezuela. Previously, a multicenter study conducted in 52 hospitals from the 12 aforementioned counties were performed during the period of July 2002–September 2006, with total of 15,156 individuals diagnosed with venous thromboembolism; 3,410 of subjects in United States and 11,746 in other countries. The patients' age range were 52–79 years old with median of 68 years old; the majority of the patients were females (50.6% vs. 49.4%). Compared to the previous study, this study had lower median (51 years old) and range for age (18 – 85 years old). The patients in our study were predominantly male (56% vs. 44%).[10,11]

In this study, 22.8% of patients had high risk for venous thromboembolism with 64.9% of the patients had received medication (UFH or LMWH) for thromboprophylaxis. In comparison with other studies, less number of patients were at high risk for thromboembolism despite the higher rate of thromboprophylaxis medication. In other study, 52% patients in United States and 43% patients in other countries had moderate to high risk for venous thromboembolism. There were 7,640 (50%) patients that had received either medical or mechanical thromboprophylaxis. There were 33% patients in United States and 47% patients in other countries that had received UFH or LMWH as thromboprophylaxis. The study had suggested several factors that may be associated with lower usage of thromboprophylaxis, notably the lack of awareness regarding thromboprophylaxis usage, lack of thromboprophylaxis algorithms in the said institution, and risk of bleeding that may occur during thromboprophylaxis procedure.[10-12]

Other countries, in contrast, had preferred the usage of LMWH compared to UFH (82.1% vs. 17.9%). Overall, higher usage of LMWH was found in the study compared to the UFH usage (74.8% vs. 25.2%). In our study, the vast majority of the patients were treated with UFH (91.7% vs. 8.35). The choice for medical thromboprophylaxis were similar with studies from United States, which UFH usage was preferred compared to LMWH in thromboprophylaxis. Costs in utilizing LMWH was not significantly different compared to usage of UFH, thus, LMWH may be safer that UFH, particularly in minimizing the risk of heparin induced thrombocytopenia (HIT).[10-14]

In this study, there were 75.9% patients with low risk (score <7) and 24.1% patients with high risk (score $\geq$7) for bleeding. In comparison, a retrospective study consisted of 12,082 subjects from Academic Health System in United States during the period of October 1, 2012–July 31, 2014, had found the majority (81% vs. 19%) of the patients had low risk of bleeding. Other study had noted that 90.3% of patient had low risk for bleeding and 9.7% had high risk for bleeding. The results of these studies concur with our study, that the majority of the patients in Hasan Sadikin General Hospital had low risk for bleeding.[7]

According the previous study from Academic Health System, bleeding had occurred on 2.6% patients with venous thromboembolism, with 1.8% patients had major bleeding (defined as bleeding that cause decrease of hemoglobin $\geq$2 g/dL or may require 2 units of blood transfusion). Major bleeding may occur as intracranial, intraocular, adrenal gland, and/ or pericardial hemorrhage. In other studies, 3.2% of patients had suffered from bleeding after thromboprophylaxis therapy, with 1.2% of these patients had suffer from major bleeding.[7] In contrast, no cases of bleeding

after thromboprophylaxis therapy were found on our patients.

In this study there were 162 subjects with mean age 51 years old. Most of subjects were male (56% vs. 44%). There were 22.8% of patients had high risk for venous thromboembolism with 64.9% of the patients had received medication (UFH or LMWH) for thromboprophylaxis. There were 75.9% patients with low risk (score <7) and 24.1% patients with high risk (score ≥7) for bleeding.

The majority of inpatients had low risk for both venous thromboembolism and bleeding. The administration of thromboprophylaxis is still uncommonly performed, only given in 14.8% subjects. Thromboprophylaxis was given in 88.9% of high risk patients for venous thromboembolism .The majority of patients with high risk of venous thromboembolism received UFH as thromboprophylaxis medication.

References

1. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. The Lancet. 2012;379(9828):1835–46.
2. Members ATF, Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, *et al.* 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC) Endorsed by the European Respiratory Society (ERS). Eur Heart J. 2014;35(43):3033–80.
3. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):3–14.
4. Goldhaber SZ. Venous thromboembolism: epidemiology and magnitude of the problem. Best Pract Res Clin Haematol. 2012;25(3):235–42.
5. Delluc A, Tromeur C, Le Ven F, Gouillou M, Paleiron N, Bressollette L, et al. Current incidence of venous thromboembolism and comparison with 1998: a community-based study in Western France. Thromb Haemost. 2016;116(11):967–74.
6. EINSTEIN–PE Investigators, Büller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, *et al.* Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):1287–97.
7. Rosenberg DJ, Press A, Fishbein J, Lesser M, McCullagh L, McGinn T, *et al.* External validation of the IMPROVE Bleeding Risk Assessment Model in medical patients. Thromb Haemost. 2016;116(3):530–6.
8. Spyropoulos AC, Anderson Jr FA, FitzGerald G, Decousus H, Pini M, Chong BH, *et al*. Predictive and associative models to identify hospitalized medical patients at risk for VTE. Chest. 2011;140(3):706–14.
9. Spyropoulos AC, Raskob GEJTH. New paradigms in venous thromboprophylaxis of medically ill patients. 2017;117(9):1662–70.
10. Decousus H, Tapson VF, Bergmann J-F, Chong BH, Froehlich JB, Kakkar AK, *et al*. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. Chest. 2011;139(1):69–79.
11. Rosenberg D, Eichorn A, Alarcon M, McCullagh L, McGinn T, Spyropoulos AC. External validation of the risk assessment model of the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) for medical patients in a tertiary health system. J Am Heart Assoc. 2014;3(6):e001152.
12. Abdel-Razeq H. Venous thromboembolism prophylaxis for hospitalized medical patients, current status and strategies to improve. Ann Thorac Med. 2010;5(4):195-200.
13. Nagase Y, Yasunaga H, Horiguchi H, Hashimoto H, Shoda N, Kadono Y, *et al*. Risk factors for pulmonary embolism and the effects of fondaparinux after total hip and knee arthroplasty: a retrospective observational study with use of a national database in Japan. Bone Joint Surg Am. 2011;93(24):e146.
14. Junqueira DR, Zorzela LM, Perini E. Unfractionated heparin versus low molecular weight heparins for avoiding heparin-induced thrombocytopenia in postoperative patients. Cochrane Database Syst Rev. 2017;4(4):CD007557.

Intracranial Metastasis as the Initial Presentation of a Young Woman with Luminal B Her-2 Positive Stage 4 Breast Cancer

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Abstract

Objective: Breast cancer is the second most common cause of brain metastasis (BM) among all of the solid cancers, with metastases occurring in 10%–16% of patients and in as many as 30% of autopsy studies. Breast cancer-related BM usually has a poor prognosis and survival rate in the absence of any treatment within 2 months. Survival after BM is related to the subtype of the primary tumor. Human epidermal growth factor-2 (HER-2)-positive patients have a significantly better prognosis compared with other subtypes. The prognosis for the majority of patients with BM remains poor, despite local and systemic therapies, with a median survival of around 10 months.

Methods: This case is interesting because our patient is very young, diagnosed with BM before breast cancer was identified, bit still surviving 12 months after her BM diagnosis. A 19-year old woman presented with seizures, vomit and headaches.

Results: A cranial CT-scan showed an intracranial mass. The intracranial tumor was removed, and yielded a histopathological result of metastatic adenocarcinoma. Further examination found a lump in her right breast. She was diagnosed with intracranial metastatic stage 4 luminal B Her 2(+) breast cancer. She was referred for WBRT, a mastectomy, chemotherapy with docetaxel cyclophosphamide 4 cycles, followed by 12 cycles of trastuzumab, and continued treatment with tamoxifen and goserelin. The last PET-Scan showed no residual disease.

Conclusion: Breast cancer as the primary tumor should be considered in women with a metastatic brain tumor. With appropriate treatment, even stage IV luminal B breast cancer with BM can still have a long life with good quality.

Keywords: Breast cancer, brain metastasis, central nervous system (CNS)

Introduction

Advanced Breast Cancer (ABC) comprises both locally advanced breast cancer (LABC) and metastatic breast cancer (MBC). Although treatable, MBC remains an incurable disease with a median overall survival (OS) of three years and a 5-years survival of only 25%. The

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development of brain metastases (BM) is one of the major challenges for patients with stage III and IV breast cancer. In a recent study, brain metastases-free survival differed significantly between breast cancer subtypes and was shortest in patients with triple receptor-negative cancer. Central nervous system (CNS) metastases account for the majority of malignant brain tumors, and may appear either within the brain parenchyma or along the leptomeninges. Breast cancer is the second most common cause of CNS metastases, and is the solid tumor most commonly associated with leptomeningeal metastases. [1,2]

On the basis of case series from the 1960s

and 1970s, the incidence of clinically evident brain metastases among women with stage IV breast cancer is estimated to be 10% to 16%. These figures underestimate the true incidence, given that brain metastases are found in 30% of patients at autopsy. Parenchymal brain metastases typically follow a vascular distribution, consistent with a mechanism of hematogenous spread. Supratentorial lesions are more common than infratentorial lesions, and there is a predilection for vascular border zones and the gray and white matter junction. In contrast, leptomeningeal metastases arise via multiple pathways, including hematogenous spread, direct extension, and infiltration from vertebral metastases via Batson's plexus. Involvement of the leptomeninges is less common clinically than parenchymal metastases, and is found in 5% to16% of patients at autopsy.[3,4]

Young age appears to be a risk factor for the development of CNS metastases. For example, in an autopsy review of 1,044 patients with breast cancer, the median age of patients with CNS metastases was about 5 years younger than that of patients without CNS metastases. Several groups have also found an association between the hormone receptor status and the incidence of CNS relapse, although these studies generally have been small in scale. In one study of 217 women with primary breast cancer, estrogen receptor (ER)–negative breast cancers were more likely to metastasize to the brain (10% vs 4% clinical incidence). In an autopsy study of 25 patients, ER-negative tumors were also more likely to metastasize to the leptomeninges. Whether this observed association relates to the inherent biology of ER-negative tumors, the ability of hormonal therapy to penetrate the CNS (thereby providing a relative risk reduction for ER-positive tumors), and/or the inverse relationship between the hormone receptor and the HER2 status is unclear on the basis of the available evidence. The association of CNS metastases with the human epidermal growth factor receptor 2 (Her2) overexpression merits special mention. An amplification of HER2 is present in 25% to 30% of human breast cancers and correlates with diminished disease-free and overall survival. Among 319 women with primary breast cancer, HER2 overexpression was the strongest predictor of the site of the first relapse in a multivariate model, with a 4.3% vs 0.4% incidence of brain metastases.[3,5]

The most common presenting symptom of parenchymal brain metastases is a headache, occurring in 24% to 48% of patients. Other common manifestations include mental status changes and cognitive disturbances, which are present in 24% to 34% of patients.[6]

This case is interesting because our patient is very young, presenting with BM before her breast cancer diagnosis, but still surviving 21 months after her BM diagnosis.

Case

In April 2018, a 19-year-old woman came to our hospital with seizures, blurred eyes, headaches and vomiting. She consulted a neurosurgeon and underwent a brain CT-scan on the 3rd of April, 2018. The CT-scan revealed a multilobulated tumor mass with cystic components on the edges including right ventricular posterior pericocalus / right parietal lobe and the medial right occipital lobe (size ± 4.54x3.88x4.27 cm) accompanied by extensive perifocal edema vitalizing the posterior right lateral and ventricular III ventricles and a mild midline shift to the left as much as ± 0.76 cm pushing the midbrain to anterior inferior, suggestive of a high-grade glioma. There were also multiple lacunae / ischemic degeneration lesions in the white frontal lobe white matter. There was no acute infarction, bleeding, vascular malformations or intracranial space occupying lesions. A craniotomy with a biopsy was performed. Histopathology showed metastatic of papillary adenocarcinoma with difficulty in ascertaining its origin. The patient was then treated with whole brain radiotherapy (WBRT). While undergoing WBRT, the patient was referred to medical oncology for further evaluation of the primary tumor. A palpable 4-cm hard, painless mass was found in the lower right quadrant of her right breast. She had had a lump in her right breast since November 2017 but it had not been evaluated. She had had menarche at the age of 11 and her grandmother had suffered from breast cancer. A positron emission tomography (PET) scan was carried out and showed an irregular mass in the lower right quadrant of the medial right breast with central necrosis accompanied by metabolic activity at the periphery, highly suggestive of malignancy. A hypermetabolic lobulated mass in the right parietooccipital surrounded by the peripheral area of the edema and pressing the posterior to the right lateral ventricle is consistent for a metastasis. No hypermetabolic lesions were seen in the lymph nodes or other organs suggestive of malignancies / other metastases. A reevaluation of the intracranial

biopsy tissue showed malignant tumor forming papillary structures section of the anaplastic cells with rounded and pleomorphic nuclei, hyperchromatic, a moderate amount of cytoplasm, the mitotic count was twenty two per ten high power field (22/10 hpf). The differential diagnosis were metastatic adenocarcinoma and anaplastic ependymoma.

She underwent an incisional biopsy on her breast lump. Breast histopathology showed a malignant breast tumor invading stroma and fat. The tumor was composed of anaplastic epithelial cells with marked pleomorphic nuclei (score 3), coarse chromatin and prominent nuclei, the mitotic count was twenty five per ten hpf (score 3), arranged in solid clusters (tubular structures <10%, score 3), with necrosis in the central part of the tumor. There were ductal carcinoma insitu foci in peripheral parts of the tumor, mostly solid types with a few comedo types, high grade. Lymphovascular and perineural invasion were not found. Immunohistochemistry staining showed estrogen receptor (ER) positive of 80%, weak to moderately stained, progesterone receptor (PR) positive of 5% weak stained, Her-2 +3 for the herceptest score and a Ki67 expression of 75% (An invasive breast carcinoma of no special type pathological grade III luminal B, Her2 positive). The patient underwent a right mastectomy which showed metastasis in 1 of 5 axillary lymph nodes. She underwent 4 cycles of chemotherapy with docetaxel and cyclophosphamide and 12 cycles with trastuzumab. In September 2018, the patient continued therapy with tamoxifen. In October 2018, a PET-scan showed no residual disease. The patient continued treatment with tamoxifen and goserelin and has since remained in remission.

Discussion

Generally, patients having breast cancer brain metastases (BCBM) is associated with a poor prognosis. The outcome for these patients remains poor even after chemotherapy and radiotherapy. Most BCBM patients are characterized by rapid growing, hormone receptor negative and/or Her-2 positive tumors concurrent with visceral metastases.[7] Breast cancer is divided into three distinct diseases with heterogeneous expression of estrogen receptor/progesteron receptor (ER/PgR) and Her2 status. Luminal type cancers, which are ER/PgR positive without a Her2-positive status, tend to be the most favorable for long-term survival. Whereas, the triple negative subtype (basal-like) and Her2-positive tumors are the most sensitive to chemotherapy, but have the poorest prognosis. Of women diagnosed with advanced breast cancer, 10% to 16% develop central nervous system (CNS) metastases. Several risk factors have been associated with the development of CNS lesions in patients with MBC, including being of a younger age (<50 year), having more than two metastatic sites at MBC diagnosis, and being Her2-positive. Patients with Her2-positive MBC tumors are 2 to 4 times more likely to develop CNS tumors than patients who are Her2-negative. The proportion of patients with brain metastases in triple-negative, Her2-positive status and luminal subtypes was 28%, 53% and 19%, respectively. This indicates that triple-negative and Her2-positive breast cancer have a special predisposition to metastasize to the brain.[8] In one study, Mauer C et al., found that the median OS for BC without BM was 46.7 months (IQR 23.0–145.6 months) and for BCBM patients 20.8 months (IQR 5.36-not reached). Patients without CNS symptoms at the time of their BM diagnosis had a better OS than patients with clinical signs related to their BM (HR 0.49, 95% CI 0.25 to 0.94).[9]

CNS involvement typically occurs late in the course of metastatic breast cancer. In most cases, the involvement of the lungs, liver, or bone precedes the diagnosis of CNS metastasis.[10]

In this case, CNS metastasis was the first discovery so the patient underwent WBRT. At present, there is no evidence that early detection of brain metastases alters the chances of survival or the quality of life of patients with breast cancer, although no prospective studies have specifically addressed this issue. Conversely, although corticosteroids, WBRT, surgery and stereotactic radiosurgery (SRS) can provide excellent palliation of some symptoms, motor loss and other focal deficits are frequently not fully reversible. Therefore, it is possible that early detection may improve the quality of life by identifying patients for treatment before irreversible neurologic damage has occured. For many years, chemotherapy and endocrine therapy have not been considered as playing a role in the treatment of patients with brain metastases because of the presence of the blood-brain barrier (BBB). Most chemotherapy agents used in the treatment of breast cancer either do not cross an intact BBB, or are pumped out of the CNS by phosphoglycoprotein in the endothelial cells comprising the BBB. They may not reach sufficient therapeutic levels to treat CNS

metastases. The finding that chemotherapy and trastuzumab treatment are associated with improved survival even after adjusting for relevant variables in patients after the development of CNS metastases is interesting. The studies have proved the permeability of the blood–brain barrier in patients with brain metastases and in patients after WBRT. It has also been observed that systemic therapy carried out after WBRT prolongs survival due to the control of extracranial disease. Actually, after WBRT of brain metastases, the blood–brain barrier is, in part, disrupted so that many chemotherapeutics and hormonal agents may reach a therapeutic level in tumors.[11]

Trastuzumab in combination with chemotherapy significantly improves OS and disease-free survival in Her2-positive BC.

The median overall survival (OS) for BCBM patients treated with whole brain radiotherapy (WBRT) alone is poor being of less than 6 months. More recent analyses suggest that the prognosis of BCBM patients, especially those with Her2-positive BCBM is improving which is probably a result of better systemic treatment options leading to better control of the disease outside the central nervous system (CNS).[12,13]

This case suggests that appropriate treatment with whole brain radiotherapy followed by trastuzumab combined with chemotherapy remains the best option for giving a long, good quality life to patients who present with brain metastasis in luminal B Her2-positive stage IV breast cancer.

References

1. Cardoso F, Costa A, Norton L. ESO-ESMO 2nd International Consensus Guidelines for advanced breast cancer (ABC2). Ann Oncol. 2014;25(10): 1871–88.
2. Cardoso F, Spence D, Mertz S, Corneliussen-James D, Sabelko K, Gralow J, *et al*. Global analysis of advanced/metastatic breast cancer: decade report (2005–2015). Breast. 2018;39:131–38.
3. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. 2004;22(17):3608–17.
4. Lee Y-T. Breast carcinoma: Pattern of metastasis at autopsy. J Surg Oncol. 1983;23:175–80.
5. Boogerd W, Vos VW, Hart AAM. Brain metastases in breast cancer; natural history, prognostic factors, and outcome. J Neuro Oncol. 1993;15:165–74.
6. Lassman AB, DeAngelis LM. Brain metastases. Neurol Clin. 2003;21(1):1-vii.
7. Cagney DN, Martin AM, Catalano PJ, Redig AJ, Lin NU, Lee EQ, *et al*. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. Neuro Oncol. 2017;19(11):1511–21.
8. Weil RJ, Palmieri DC, Bronder JL, Stark AM, Steeg PS. Breast cancermetastasis to the central nervous system. Am J Pathol. 2005;167:913–20.
9. Maurer C, Tulpin L, Moreau M, Dumitrescu C, Azambuja Ed, Paesmans P, *et al*. Risk factors for the development of brain metastases in patients with HER2positive breast cancer. ESMO Open. 2018;3:e000440.
10. Engel J, Eckel R, Aydemir U, Aydemir S, Kerr J, Schlesinger-Raab A, *et al*. Determinants and prognoses of locoregional and distant progression in breast cancer. Int J Radiat Oncol Biol Phys. 2003;55(5):1186–195.
11. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. J Clin Oncol. 2004;22:3608–617.
12. Brufsky AM, Mayer M, Rugo HS, Tan CE, Tripathy D, Tudor IC, *et al*. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. Clin Cancer Res. 2011;17(14):4834–43.
13. Dawood S, Broglio K, Esteva FJ, Buzdar AU, Hortobagyi GN, Giordano HG. Defining prognosis for women with breast cancer and CNS metastases by HER2 status. Ann Oncol. 2008;19(7):1242–48.

Length of Stay Children Hospitalized with Chronic Kidney Disease Based on Etiology and Stage in Dr. Hasan Sadikin Hospital Bandung, Indonesia

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Abstract

Objectives: This study aims to describe the LOS children hospitalized with CKD based on the etiology and stage at Dr. Hasan Sadikin General Hospital, Bandung in 2016–2018.

Methods: This was a retrospective study with a cross-sectional design from June–October 2019. The inclusion were all medical records of pediatric inpatient diagnosed with CKD and exclusion criteria were incomplete medical record data and hospital readmission patients. The variables studied were CKD etiology, CKD stage, and length of stay

Results: From 103 patients, the etiologies found were steroid-resistant nephrotic syndrome (SRNS) (58.25%), congenital anomalies of kidney and urinary tract (9.71%), urinary tract infection (5.83%), and chronic glomerulonephritis (21.36%). The mean LOS was 19 days. The longest LOS found in CKD stage 5 patients caused by SRNS (141 days). Meanwhile, the shortest LOS was found in CKD stage 2 patients caused by chronic glomerulonephritis and CKD stage 5 patients were caused by SRNS who died (1 day).

Conclusion: Pediatric patients with CKD stage 5 with SRNS has the potential to have a longer LOS than other etiologies.

Keywords: Children, chronic kidney disease, etiology, length of stay, stages

Introduction

Chronic Kidney Disease (CKD) is an abnormal condition in the structure or function of the kidney, which occurs for more than three months, with health implications.[1] CKD is classified according to decreased function of the glomerular filtration rate (GFR) and albuminuria levels.[1] There are 11–12 new CKD cases per 1,000,000 children in Europe with a prevalence of 55–60 cases per 1,000,000 children.[2] The incidence continues to increase compared to previous years.[3]

The Kidney Disease Outcomes Quality Initiative (KDOQI) divides the classification of CKD into 5 stages. The stage of CKD is determined by the level of decline in kidney function, namely through GFR.[4] GFR levels are categorized as normal if >90mL/min/1.73 m^2. The lower the GFR levels, the higher the CKD stages. All individuals with GFR levels <60mL/ min/1.73 m^2 for ≥3 months have been diagnosed with CKD, with or without kidney damage.

The main causes of CKD in children are different from adults. In children, CKD is usually caused by congenital anomalies of the kidney and the urinary tract (CAKUT) (49.1%), steroid-resistant nephrotic syndrome (SRNS) (10.4%), chronic glomerulonephritis (e.g. lupus nephritis, Alport's syndrome) (8.1%) and renal ciliopathy (5.3%).[2] Some other causes of CKD in children are microangiopathic thrombosis, nephrolithiasis, Wilms tumor, infection, and others. The etiology of CKD will determine the progression of CKD severity. In

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some CKD cases, continuous kidney structure damage can cause End Stage Renal Disease (ESRD).[6] Patients with ESRD conditions require renal replacement therapy (RRT) in the form of hemodialysis, peritoneal dialysis, or transplantation to stay alive.[6] Patients with RRT require high costs of hospitalization.[7]

Data obtained in 2015 showed that Indonesian health insurance, Badan Penyelenggara Jaminan Sosial (BPJS), financing for kidney failure was IDR 2.68 trillion.[8] This was ranked the second largest financing after the heart disease.[8] However, there are often differences in the calculation of hospital cost which the hospital fee rates are greater than the Indonesia Case Base Groups (INA-CBGs) rates.[9] Difference in rates may not be charged on patients (Kemenkes RI, 2014). If this happens continuously, it will cause harm to the hospital. The long length of stay (LOS) will add up the financial burden of health services. Identification of factors related to LOS in children with CKD, the etiology and stage of the CKD can help in determining interventions to reduce the LOS.

This study aims to look at the differences of LOS in children with CKD based on their etiology and stage of disease. From this study, it is expected to be able to provide an overview data about the LOS in CKD patients. The data can help the hospital and BPJS in determining alternative treatments that are more effective and efficient of cost by considering the LOS of pediatric patients with CKD, as well as being the basic consideration for BPJS in determining INA-CBGs rates for children with CKD patients.

Methods

This study was a retrospective study with a cross-sectional design, conducted from June to October 2019 using secondary data from the medical record database in Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. The subjects of this study were pediatric patients who were hospitalized in Hasan Sadikin General Hospital, Bandung in 2016–2018. The inclusion criteria of this research were all medical records of children patients diagnosed with Chronic Kidney Disease treated in Dr. Hasan Sadikin General Hospital Bandung, Indonesia and exclusion criteria were inaccessible or incomplete registry data and hospital readmission patients.

Data was taken from the patient's medical record with total sampling method, and processed using Microsoft Excel 2010. Data collection was carried out after obtaining ethical approval number 244/UN6.C1.1/DL/2019 by the Research Ethics Committee of Universitas Padjajaran Bandung, and Research Licensing Letter issued by the Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung (No. LB.02.01/X.2.2.1/10525/2019). The selected data will be presented in the table to illustrate the difference in LOS.

Results

Based on the list of names given from the medical record database, the total pediatric CKD patients who were hospitalized in Dr.
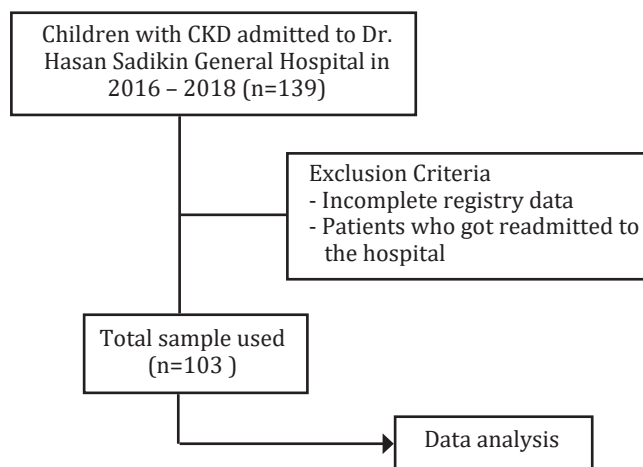

Fig. Diagram of Subject Selection

Table 1 Characteristics of Children with CKD

Characteristics	(n=103)	%
Sex		
Male	56	54.37
Female	47	45.63
Age Group		
1–5 years	9	8.74
6–9 years	11	10.68
10–18 years	83	80.58
Funding Sources		
Private	7	6.80
BPJS Non-PBI	55	53.40
BPJS PBI	34	33.01
Hospital subsidy	7	6.80

Hasan Sadikin General Hospital, Bandung in the study period was 139 people, but there were 7 inaccessible data. There were 103 data meet the inclusion criteria from 132 data that have been collected. A total of 29 data were excluded because they were patients with readmission hospitalization.

Characteristics of pediatric CKD patients treated at Dr. Hasan Sadikin General Hospital can be seen in Table 1. Out of 103 patients, the majority of the patients were male (54.37%), adolescent (80.58%), and had funding sources from BPJS (86.41%), which includes BPJS non-PBI (53.40%) and PBI (33.01%). The oldest patient in this study was 18 years old and the youngest one was 1 year old with an average age of 12 years.

In this study, the most frequent etiology was SRNS. The longest LOS in this group was 141 days with an average LOS of 22 days. Patients with CAKUT were mostly hospitalized for 8–14 days (40.0%). While most of the patients with chronic glomerulonephritis were hospitalized for ≤7 days (40,91%). Half of the patients with urinary tract infection (UTI) had to be hospitalized for 15–21 days. Patients with other etiology such as renal tuberculosis mostly had LOS in the 8–14 days group (60.0%). Overall, the mean LOS in all patients was 19 days with the longest LOS was 141 days in patients with SRNS. The shortest LOS was found in patients with CKD stage 2 caused by chronic glomerulonephritis who got hospitalized for 1 day and patient with CKD

Table 2 Length of Stay of Children with CKD based on Etiology

Characteristics	CKD Stages (n=103)				
	CAKUT n (%)	SRNS n (%)	Chronic Glomerulo-nephritis n (%)	Urinary Tract Infection n (%)	Others n (%)
Length of Stay					
≤7 days	2 (20.0)	18 (30.0)	9 (40.91)	1 (16.67)	1 (20.0)
8–14 days	4 (40.0)	10 (16.67)	3 (13.64)	1 (16.67)	3 (60.0)
15–21 days	1 (10.0)	7 (11.67)	7 (31.81)	3 (50.0)	0 (0.0)
22–28 days	1 (10.0)	8 (13.33)	1 (4.55)	1 (16.67)	0 (0.0)
>28 days	2 (20.0)	17 (28.33)	2 (9.09)	0 (0.0)	1 (20.0)

Tabel 3 Length of Stay of Children with CKD based on Stage

Characteristics	CKD Stages (n=103)				
	Stage 1 n (%)	Stage 2 n (%)	Stage 3 n (%)	Stage 4 n (%)	Stage 5 n (%)
Length of Stay					
≤7 days	6 (60.0)	1 (50.0)	2 (40.0)	1 (50.0)	21 (25.0)
8–14 days	0 (0.0)	1 (50.0)	1 (20.0)	1 (50.0)	18 (21.43)
15–21 days	3 (60.0)	0 (0.0)	1 (20.0)	0 (0.0)	14 (16.67)
22–28 days	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	10 (11.90)
>28 days	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	21(25.0)

stage 5 caused by SRNS who died.

Research data shows that from 103 patients, 84 of them suffered CKD stage 5. The majority of CKD patients have LOS in the category ≤7 days (60%). Similarly, in patients with CKD stages 2, 3, and 4, the most LOS is ≤7 days which is 50%, 40%, and 50%, respectively. Whereas patients with CKD stage 5 have an equivalent percentage in the ≤7 days and >28 days category, which is 25%. Patients with CKD stage 5 have an average LOS of 21 days with the longest stay was 141 days.

Discussion

In this study we found that children with CKD were more prevalent in males (54,35%). This finding is similar to the previous studies conducted by Becherucci et al.[2] This is due to the higher incidence of congenital disorders, one of the most common etiology of CKD in children, including obstructive uropathy and renal dysplasia in males than in females.[10] Similarly, the prevalence of ESRD was more prevalent in males than females. This data is in accordance with a previous study which states that the progression of CKD in men is faster than in women.[11,12] This is likely caused by estrogen hormone in female which act as a protective agent, while in men there is the testosterone hormone which is damaging to the kidneys.[12]

The incidence of CKD increases with age. 80,58% of the patients were in the 10–18 years age group with the most common etiology was SRNS. This is similar to the data obtained from 14 Educational Hospitals with Children's Nephrology Consultants (2017). In patients aged 1-5 years old, the most common etiology was CAKUT. This is in accordance with a study that has been done previously in Tunisia.[13]

The etiologies of pediatric CKD patients in this study were SRNS, CAKUT complicated by UTI, and chronic glomerulonephritis. SRNS patients need time for hemodynamic stabilization of the patient, diagnosis, and administration of chemotherapy.[14] However, the process of finding the best therapy for patients with SRNS is individual, so the duration of LOS and the outcome of each patient can be different.[14] The LOS of patients with CAKUT in this study were mostly in the 8–14 days category (40%). Patients with congenital anomalies will undergo the correction procedure for these abnormalities.[15] In patients with CAKUT who complicated by UTI, patients need time to manage the UTI that require a minimum of

10 days for antibiotics, and a minimum of 3–7 days to obtain urine culture results. Imaging examinations (radiology) are also needed to establish the diagnosis and determine the next steps of management.[15] As for patients with an initial etiology of UTI, the bacterial culture will be performed on patients and then given antibiotics. Chronic glomerulonephritis also requires a quite long hospitalization, but not requires chemotherapy or surgery.

The LOS of children with stage 5 CKD is mostly in ≤7 days and> 28 days category. The difference was caused by the condition of some patients who experienced hemodynamic instability so the doctor must wait for the patient to return stable to start the treatment. In addition, the setting-up device for hemodialysis or peritoneal dialysis will take several days. This will complicate the treatment process and have an impact on the LOS of the patient. However, not all CKD stage 5 patients experience this condition so that the doctor can start kidney replacement therapy and send the patient home when his condition has improved. Some of the patients with CKD stage 5 admitted because the doctors found other disorders, such as anemia and pulmonary edema during hemodialysis. In this condition, the patient needs to be hospitalized for a few days until the patient gets better. Eighteen patients with CKD stage 5 died in this study, either by the progression of the disease or by the other comorbid the patients had. Death is one of the factors that affect the LOS, which can reduce the duration of stay.

The LOS in patients with CKD stage 2, 3, and 4 were not as long as patients with CKD stage 5. The majority of first-stage CKD patients were hospitalized for ≤7 days because generally, the patient is not in life-threatening condition, so patients can be discharged immediately after being treated. In those patients, clinical monitoring will be carried out in the form of vital signs and supporting examinations to determine the patient's overall condition. If the patient is found contraindicated for treatment (anemia, leucopenia, thrombocytopenia), then the correction will be carried out first before starting therapy.

In addition to the etiology and stage of the disease, there are other factors influence the LOS of patients with CKD in children. In this study, several patients went home before achieving recovery for various reasons both financial and family reasons. This is supported by Nursalam's study which states the reason for leaving a patient can affect the LOS of the patient. Other studies also confirmed that

patient condition at discharge affected LOS.[16] In the present study, the patient's condition at discharge was unclear because it was not stated in the medical record, unless if the patient dies. This may affect the LOS of patients in this study.

In the patient funding source data, the majority of patients pay with governmental insurance (BPJS), PBI and non-PBI. A study in Iran states that the method of payment affects the LOS of patients with the results of patients who use health insurance have a longer stay than patients with independent payments.[17,18]

The limitation of this study is inaccessible registry data from the hospital system due to the transfer of paper-based data to paperless. Besides, the limited time of the study also caused a reduction in the sample taken in this study, causing an uneven distribution of the number of members in each group of data.

For further research it is recommended that the recording of data registers can be done more carefully. Besides, further research is expected to increase the number of samples by extending the period so that the data collected can better present each group of data. A multicentre study in various regions is also needed to obtain data that better represents the LOS of pediatric CKD patients throughout Indonesia.

It can be concluded that from 103 patients with CKD at Dr. Hasan Sadikin General Hospital Bandung in the 2016–2018 period, the majority of the patients are male, adolescent, and have sources of funding from BPJS, PBI and non-PBI. CKD with SRNS has the potential to prolong the LOS, so the patients will need greater costs. In patients with CKD stage 5, the duration of LOS is longer because most patients experience hemodynamic disorders that require stabilization before starting treatment.

References

1. KDIGO. Clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease. Kidney Int Suppl. 2017;7(3):e1.
2. Becherucci F, Roperto RM, Materassi M, Romagnani P. Chronic kidney disease in children. Clin Kidney J. 2016;9(4):583–91.
3. Wong CJ, Moxey-Mims M, Jerry-Fluker J, Warady AB, L. Furth S. CKiD (CKD in Children). NIH Public Access. 2013;60(6):1002–11.
4. Initiative NKF (NKF) KDQ. Clinical Practice Guidelines. New York: National Kidney Foundation; 2002.
5. Pardede SO, Chunnaedy S. Penyakit ginjal kronik pada anak. Sari Pediatr. 2017;11(3):199.
6. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. Kidney Int. 2011;80(12):1258–70.
7. El Nahas AM, Bello AK. Chronic kidney disease: The Global Challenge. Lancet. 2005;365 (9456):331–40.
8. Kemenkes RI. Situasi penyakit ginjal kronis. Pus Data dan Inf Kementerian Kesehatan RI. 2017.
9. Azalea M, Andayani TM. Analisis biaya pengobatan penyakit ginjal kronis rawat inap dengan hemodialisis di rumah sakit. J Manaj dan Pelayanan Farm. 2016;141–50.
10. Warady BA, Chadha V. Chronic kidney disease in children: the global perspective. Pediatr Nephrol. 2007;22(12):1999–2009.
11. Goldberg I, Krause I. The role of gender in chronic kidney disease. Eur Med J. 2016;1(2):58–64.
12. Carrero JJ, Hecking M, Chesnaye NC, Jager KJ. Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. Nat Publ Gr. 2018; Available from: http://dx.doi.org/10.1038/nrneph.2017.181
13. Maalej B, Louati H, Guirat R, Wali M, Abid H, Jallouli M, et al. Childhood chronic kidney disease. iMedPub Journals. 2018;2(1);1–3.
14. Nourbakhsh N, Mak RH. Steroid-resistant nephrotic syndrome: past and current perspectives. Pediatric Health Med Ther. 2017; 8:29–37.
15. Sahay M. Congenital anomalies of kidney and urinary tract. Clin Queries Nephrol. 2013;2(4):156–65.
16. Sepehri A, Simpson W, Sarma S. The influence of health insurance on hospital admission and length of stay-The case of Vietnam. Soc Sci Med. 2006;63(7):1757–70.
17. Khosravizadeh O, Vatankhah S, Bastani P, Kalhor R, Alirezaei S, Doosty F. Factors affecting length of stay in teaching hospitals of a middle-income country. Electron Physician. 2016;8(10):3042-3047.
18. Gohari M, Vahabi N, Moghadamifard Z. Semi-parametric Cox regression for factors affecting hospitalization length. Daneshvar Pezeshki. 2012;19(99):23–30.

Pattern of Indirect Immunofluorescence Assay Antinuclear Antibody in Pediatric Lupus Nephritis

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Abstract

Objective: To determine the association between Anti-Nuclear Antibody (ANA) pattern in pediatric Systemic Lupus Erythematosus (SLE) patients and proteinuria as a sign of renal involvement in SLE.

Methods: This was a cross-sectional study, using data from medical records involving 89 newly diagnosed with SLE (aged ≤18 years) in Department of Child Health Dr. Hasan Sadikin General Hospital, Bandung, from January 1, 2018 to June 30, 2019. Data of ANA pattern and proteinuria were collected from medical record. ANA pattern was examined by Immunofluorescence Assay (IFA) method. Chi-square was used to analyze the association between ANA pattern and proteinuria as a sign of renal involvement in pediatric SLE patients.

Results: There were 89 patients, consisting of 7 male (7.9%) and 82 female (92.%) with median age of 14 (IQR=12–16). There were only 44 pattern of ANA as follow: homogenous 56.8%, speckled 36.4%, and nucleolar 6.8%. However, there is no significant association between homogenous pattern with proteinuria events (p=0.831).

Conclusions: Homogenous pattern was the most frequent ANA pattern in children with SLE, and the pattern has no association with proteinuria events.

Keywords: Antinuclear antibody pattern, indirect immunofluorescence assay; proteinuria, systemic lupus erythematosus

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by a loss of tolerance from the immune system and formed autoantibodies. The autoantibody also known as Anti-Nuclear Antibody (ANA) which have many subtypes that can attack self-antigens and cause inflammation in several organs, such as skin, joints, kidneys, blood-forming cells, blood vessels, and central nervous system.[1,2, 3,4] ANA test is one of tests that used for helping diagnose autoimmune disorder. Patients with SLE are almost always positive for ANA, meanwhile patients with other autoimmune disoreders who have positive ANA result are varies, even a significant number patients with other types of disorders and some healthy people might have positive ANA, especially at low levels. Moreover, American College of Rheumatology (ACR) 1997 recommends Immunoflourecence Assay (IFA) method as a gold standard of ANA test which can help clinician to diagnose the autoimmune disorder more specifically besides another manifestations showed by the patient. It can also help to reduce risk of false positive or errorneous.[1] By the result of the test, the clinician might see the titers and different types of ANA through the staining pattern. Based on International Consensus of ANA Pattern (ICAP), ANA is divided into

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three major categories, namely nuclear (such as homogeneous, speckled, centromere, nucleardots and nucleolar), cytoplasmic and mitotic patterns. The results of the titer and ANA pattern will be varied in each patients.[7,15,16]

Systemic Lupus Erythematosus can occur in both adults and children. However, when compared with adults, children and adolescents have a higher risk of severity and involvement of other organs as a manifestation in SLE.[5,6] The most common and difficult manifestation of SLE is renal involvement. The involvement of the renal as a clinical manifestation will cause inflammation in the renal called nephritis.[5,6,8] One of the result of the inflammation is the presence of protein in the urine, which called proteinuria. In the case of pediatric SLE, lupus nephritis is more common in females than males with a ratio of 8-13: 1 and in the age range of 14-16 years.[5] Also, pediatric SLE with nephritis having poorer prognosis than others without nephritis.[8,9]

The study about relevance of ANA in SLE has been adressed repeatedly. Through the studies, ANA is known to have a correlation with the clinical manifestations of SLE, especially in patient with positive anti-

dsDNA and/or anti-Sm. The presence of anti-dsDNA was found to be associated with renal disorder, haematological involvemnet and serositis, meanwhile patient with anti-Sm had the highest frequency of malar rash, oral ulcers, arthritis, and serositis.[18] Whereas, studies about ANA pattern and its relation with the clinical manifestation of SLE are very scarce especially proteinuria. A few studies stated, there were no association between ANA Pattern and clinical manifestation of SLE, Frodlund M et al. observed that some pattern may have an association with the clinical manifestation of SLE.[10,12,13,14] However, this finding needs more confirmation by others.[10,14,17,18]

This study is aimed to determine the association between ANA pattern in pediatric SLE patients and proteinuria as a sign of renal involvement in Department of Child Health Hasan Sadikin Bandung General Hospital.

Methods

This was a cross-sectional study conducted of 89 subejct newly diagnosed patients with Systemic Lupus Erythematosus (aged ≤18 years), in Department of Child Health Dr. Hasan Sadikin General Hospital, Bandung, from January 1st 2018 until June 30th 2019. Secondary data from medical records of newly diagnosed with SLE were used in this study. Data of age, gender, ANA pattern, and proteinuria were collected from the medical records. ANA pattern was examined by Immunoflourecence Assay Method. Data was taken after obtaining Ethical Clearance issued by Health Research Ethics Committee of Universitas Padjadjaran Bandung No. 719/UN6.KEP/EC/2019 and Research Licensing Letter issued by Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung No. LB.02.01/X.2.2.1/10047/2019. Microsoft® Excel 2013 and IBM® SPSS® Version 20 were used to process the data. Chi-square was used to analyze the association between ANA pattern and proteinuria as a sign of renal involvement in SLE and $p<0.05$ was considered statistically significant.

Results

There were 89 subjects, consisting of 7 male and 82 female with median age of 14 (IQR=12–16) (see Table 1). Besides hematological manifestation, renal was the most frequent manifestation in pediatric SLE patients (see Table 1). Pattern of ANA was analyzed and

Table 1 Characteristics of Systemic Lupus Erythematosus Patients

Characteristics	Total (n=89)
Age (years)	
Median [IQR]	14 (12–16)
Gender (n, %)	
Boys	7 (7.9%)
Girls	82 (92.1%)
Skin manifestation (n, %)	
Malar Rash	32 (44.4%)
Discoid Rash	14 (22.6%)
Photosensitivity	29 (36.7%)
Mouth Ulcers	12 (19.7%)
Renal manifestation (n, %)	
Proteinuria	46 (51.7%)
Hematuria	42 (47.2%)
Hematological manifestation (n, %)	
Anemia	61 (77.2%)
Leukopenia	19 (24.1%)
Thrombocytopenia	10 (12.7%)
Neuropsychiatric manifestation (n, %)	7 (9.2%)

Table 2 ANA Pattern of Systemic Lupus Erythematosus Patients

Category	Total (n=44)
Homogenous (n, %)	25 (56.8%)
Speckled (n, %)	16 (36.4%)
Nucleolar (n, %)	3 (6.8%)

homogenous was the most common type followed by speckled, and nucleolar (Table 2). Further data processing was performed with chi-square to assess the association between ANA pattern and proteinuria events as a sign of renal involvement in pediatric SLE patients (Table 3). There is no significant association between homogenous pattern with proteinuria events.

Discussion

Based on the study, it is known that the subjects are mostly girls. Similar with the result of other studies that have been done, one of them is study from Almaani S, et al. which stated that the most of children with SLE were girls than boys, with female-to-male ratio range between 8-13 : 1 and in the age range of 14-16 years.[5] This finding was because of hormonal factors such as sex steroids which are owned by girls, thus will increasing the risk of SLE.[1,6]

In patients with SLE, we can find the presence of ANA. ANA is autoantibodies which formed by the immune system that can attack self-antigen and cause inflammation in many tissues and organs.[1,2,3,4,5] ANA test is a primary test to determines the presence of ANA. Despite this, ACR 1997 recommends Immunoflourecence Assay (IFA) method as a gold standard of ANA test, because it can help the clinician to diagnose the patient more specifically and reduce risk of false positive or errorneous based on the results of the test. From the test, the clinician might see the titers and patterns ANA of the patient.[7,15,16,19] However, only few patients are checked for

ANA with IFA method, while the rest patients only reported whether ANA is reactive or non-reactive.[10,11]

According to the ICAP, ANA have associated with some autoimmune diseases which show based on the staining pattern. Homogeneous patterns was common in SLE, drug-induced lupus, and Juvenile Idiopathic Arthritis (JIA) patients, while speckled was common in Mixed Connective Tissue Disease (MCTD), SLE, Sjogren Syndrome (SJS), and Systemic Sclerosis (SSc) patients.[15,17] In this study, ANA pattern of the patients only homogeneous, speckled, and nucleolar. The most frequent pattern was homogeneous (56.8%) followed by speckled (36.4%), and nucleolar (6.8%). This is similar with the study of Yilmaz O et al. which reported homogenous pattern were the most common patterns, the result of the study showed that homogenous pattern in more than half of their patients.[13] But differ with the study of Ghrahani R, et al. which are speckled (40.3%) was the most frequent of ANA pattern, followed by nucleolar (16.1%), nucleardot (9.7%), and combination of nucleardot with speckled (3.2%).[10] Also, Mengeloglu Z, et al. reported speckled patterns were the most common patterns.[12]

Frodlund M et al. observed that ANA is known to have a correlation with the clinical manifestations of SLE, especially in patient with positive anti-dsDNA and/or anti-Sm. The presence of anti-dsDNA was found to be associated with renal disorder, haematological involvement, and serosis, meanwhile patient with anti-Sm had the highest frequency of malar rash, oral ulcers, arthritis, and serosis. Some ANA pattern may have an association with the clinical manifestation of SLE. Organ damage was less common among patients with speckled pattern. However, this finding needs more confirmation by others.[18]

There is no association between ANA pattern with the proteinuria events in this study. This result is similar with the study of Ghrahani R, et al. which stated that there was no association between ANA pattern

Table 3 Association between ANA Pattern and Proteinuria Events

Category	Proteinuria		p	OR (95% CI)
	Positive	Negative		
ANA Pattern (n=44)				
Homogenous	15	12	0.831[*]	0.875 (0.256–2.989)
Non - homogenous	10	7		

*chi-square test, OR: Odds Ratio, CI: Confidence Interval

with the proteinuria events with chi-square test p=0.680.[10] It can be said that there is no difference with the studies even though being conducted in the different periods and the same place. Damoiseaux J, et al stated that there are several reasons for not finding an association between the ANA pattern and the manifestations of the disease. First, determination of the patterns in laboratories is inconsistent because of the subjectivity and experienced of the staff in interpretation the results. Second, healthy individual may have autoantibodies. Third, the result of the patterns may slightly differ depending on the substrate used.[14,17]

This study had several limitations, the data was collected retrospectively and not all samples have the variables needed (i.e. Anti Nuclear Antibody Pattern),

Based on this study, we concluded that ANA can be checked by IFA. By the test, clinician might see the different types of ANA through staining pattern. In this study, homogenous pattern was the most frequent ANA pattern in patient with SLE. Renal involvement was common in children and adolescents compared to adults patient with SLE, besides hematological involvement. Involvement of the renal can cause inflammation and one of the result is the presence of proteinuria. The homogeneous pattern has no association with proteinuria events.

References

1. Vinay K, Abul KA, Jon CA. Robbins and cotran pathologic basis of disease. 9th edition. Philadelphia: Elsevier Saunders. 2014. p. 211–226.
2. Lehman TJA, Taber SF, Nuruzzaman F. Systemic lupus erythematosus in childhood and adolescence. in: dubois' lupus erythematosus and related syndromes. 9th ed. Elsevier Inc. 2018. p. 520–531.
3. Samanta M, Nandi M, Mondal R, Hazra A, Sarkar S, Sabui T, et al. Childhood lupus nephritis: 12 years of experience from a developing country's perspective. Eur J Rheumatol. 2017;4(3):178–183.
4. Kasjmir YI, Handono K, Wijaya LK, Hamijoyo L, Albar Z, Kalim H, et al. Rekomendasi Perhimpunan Reumatologi Indonesia untuk diagnosis dan pengelolaan lupus eritematosus sistemik. 2011. p. 1–54.
5. Almaani S, Meara A, Rovin BH. Update on lupus nephritis - nephrology rounds. Clin J Am Soc Nephrol. 2017;12:825–35.
6. Szymanik-Grzelak H, Kuźma-Mroczkowska E, Małdyk J, Pańczyk-Tomaszewska M. Lupus nephritis in children-10 years' experience. Cent Eur J Immunol. 2016;41(3):248–54.
7. Lam N-CV, Ghetu M V, Bieniek ML. Systemic lupus erythematosus: Primary care approach to diagnosis and management. Am Fam Physician. 2016;94(4):284–94.
8. Sinha R, Raut S. Pediatric lupus nephritis: Management update. World J Nephrol. 2017;3(2):16.
9. Zhu J, Wu F, Huang X. Age-related differences in the clinical characteristics of systemic lupus erythematosus in children. Rheumatol Int. 2013;33(1):111–15.
10. Ghrahani R, Setiabudiawan B, Sapartini G. Karakteristik Pola Antibodi Antinuklear pada Anak dengan Systemic Lupus Erythematosus serta Komplikasinya. J Indon Med Assoc. 2012;62(7:)273–76.
11. Gomez RLA, Uribe U, Uribe O, Romero HG, Cardiel MH, Wojdyla D, et al. Childhood systemic lupus erythematosus in Latin America: The GLADEL Experience in 230 children. Lupus. 2008;17(6):592–604.
12. Mengeloglu Z, Tas T, Kocoglu E, Aktas G, Karabork S. Determination of anti-nuclear antibody pattern distribution and clinical relationship. Pak J Med Sci. 2014;30(2):380–3.
13. Yilmaz O, Karaman M, Ergon MC, Bahar IH, Yulug N. Comparison of indirect immunoflourescence and enxyme immunoassay methods for the determination of antinuclear antibodies. Mikrobiyol Bul. 2014;38(1-2):85–90.
14. Damoiseaux J, Andrade LEC, Carballo OG, Conrad K, Francescantonio PLC, Fritzler MJ, et al. Clinical relevance of HEp-2 Indirect immunoflourescent patterns: the International Concensus on ANA Patterns (ICAP) perspective. Ann Rheum Dis. 2019;78:879–89.
15. Damoiseaux J, Andrade LEC, Carballo OG, Conrad K, Francescantonio PLC, Fritzler MJ, et al. International consensus on ANA patterns (ICAP): the bumpy road towards a consensus on reporting ANA results. 2016;7(1):1–8.
16. Cruvinel WdM, Andrade LEC, von Mühlen CA, Dellavance A, Ximenes AC, Bichara CD, et al. V Brazilian consensus guidelines for detection

of anti-cell autoantibodies on hep-2 cells. Adv Rheumatol. 2019;59(1):28.

17. Chan EKL, Damoiseaux J, Cruvinel WdM, Carballo OG, Conrad K, Francescantonio PLC, *et al*. Report on the second International Consensus on ANA Patterns (ICAP) workshop in Dresden 2015. Lupus. 2016;25:797–804.

18. Frodlund M, Dahlstrom O, Kastbom A, Skogh T, Sjowall C. Associations between antinuclear antibody staining patterns and clinical features of systemic lupus erythematosus: analysis of a regional Swedish register. BMJ Open. 2013;3(6):1–8.

19. Ricchiuti V, Adams J, Hardy DJ, Katayev A, Fleming JK. Automated Processing and Evaluation of Anti-Nuclear Antibody Indirect Immunofluorescence Testing. Front Immunol. 2018;9:927.

Elderly Satisfaction on Chronic Disease Management Program at Public Health Center, Bandung City, West Java, Indonesia

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Abstract

Objective: To identify the satisfaction level of the elderly on the health services provided by The Chronic Disease Management Program (*prolanis*) at the Public Health Center (*puskesmas*).

Methods: A descriptive quantitative study with a cross-sectional approach had been carried out to 112 elderly from 8 *puskesmas* in Bandung City, West Java, Indonesia. This study was conducted from August until November 2019. The variables in this study were 5 dimensions of the SERVQUAL. The collected data were analyzed using percentages and the Importance-Performance matrix.

Results: The satisfaction level of the elderly on the health services provided by the prolanis was 92%. The dimension that has the highest satisfaction level was the assurance dimension (94,6%) and the lowest one was the tangibles dimension (84,8%). The result of the importance-performance matrix showed that assurance, responsiveness, and empathy dimensions needed to be maintained to reach the patient's satisfaction.

Conclusions: The elderly satisfaction on the health services provided by the prolanis is high in every dimension of the SERVQUAL.

Keywords: Chronic disease management program, elderly, Importance-Performance matrix, satisfaction, SERVQUAL

Introduction

Indonesia has an increase in the total population of the elderly. It is reported that in 2019 there was 25.64 million elderly in Indonesia (9.60%) and this percentage is predicted to increase each year.[1] The aging process causes the elderly more susceptible to disease. The overall morbidity rate both in urban and rural areas in three consecutive years from 2013 to 2015 was 24.8%, 25.05%, and 28.62%, respectively. Stroke, malignancy, asthma, and diabetes mellitus type 2 are the common diseases occurred.[2] The Indonesian Social Security Agency in the health sector, developed a Chronic Disease Management Program (*prolanis*) for the National Health Insurance (JKN) participants, conducted especially at the public health center

(*puskesmas*). The *prolanis* is a program that organized various activities to control the chronic diseases, prevent it from reaching complications, and finally increasing the health status of the elderly.[3]

The success of the *prolanis* is still not satisfactory. The compliance level is still low.[4] The monitoring of the patient's blood sugar levels and the treatment compliance are not optimal.[5] One of the causes of this low compliance is satisfaction.[4]

Patient satisfaction is one of the indicators of the quality of care. It indicates the success of the health providers to meet the patient's expectations of the health care they received.[6] The satisfaction level can be measured through an instrument known as Service & Quality (SERVQUAL).[7,8] The study about the satisfaction level of the elderly on the *prolanis* by using SERVQUAL has not been carried out. Based on this information, the purpose of this study was to identify the satisfaction level of the elderly on the health services provided by the *prolanis* in the *puskesmas*.

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Methods

This study was a descriptive study with a cross-sectional method, conducted from August 2019 to November 2019 in Bandung City, West Java Indonesia. The total number of *puskesmas* that provided *prolanis* was 16 *puskesmas* and from that number, 50% (8 *puskesmas*) were selected by simple random sampling. The inclusion criteria were elderly aged 60 years and over, willing to participate in the study, able to communicate well, and came for treatment at the *puskesmas*, whereas the exclusion criteria were elderly that did not take the interview completely. The total samples were calculated by using sample formula for categorical descriptive study, with α=5%, and p value=0.88.[9] Based on that formula, the total samples needed in this study were 112 respondents. Before determining the number of elderly in each *puskesmas,* the researchers requested data on the presence of the elderly for 3 months in each selected *puskesmas*. This data was used as a denominator in calculating the number of samples in each *puskesmas*. The number of respondents in each *puskesmas* was calculated by the number of elderly visits at the *puskesmas* (n) divided by the total number of elderly visits to the 8 *puskesmas* (N) and multiplied by the number of samples needed. On the day of data collection, the number of the elderly present was uncertain, therefore the respondents were selected using consecutive sampling, a sampling technique in which every subject meeting the criteria of inclusion was selected until the required sample size was achieved. Permission to do the study was obtained from three institutions, namely the Bandung City Mayor Office, Bandung City Health Office, and the selected *puskesmas*. This study had received the ethical clearance from the Health Research Ethics Committee of Universitas Padjadjaran Bandung, Indonesia under the ethical clearance 1036/UN6.KEP/EC/2019.

The questionnaire of the SERVQUAL consisted of 22 statements and divided into 5 dimensions, namely tangibles, reliability, assurance, responsiveness, and empathy[7,8], and was developed by the Departement of Public Health Faculty of Medicine Universitas Padjadjaran in 2011, based on the SERVQUAL by Parasuraman. It was tested to 53 respondents from Bandung City. A content and construct analysis were carried out. The result of the Cronbach's alpha was between 0,801 and 0,977 for each dimension.[10] The tangibles dimension consisted of 4 statements, namely visually appealing rooms; complete facilities; employees who have a neat, professional appearance; and complete medical equipment. The reliability dimension consists of 5 statements, namely, providing services as promised; dependability in handling customers' problems; simple procedures; providing services at the promised time; and prompt administrative services. The assurance dimension consisted of 4 statements, namely health providers who instill confidence in customers; making customers feel safe; respect the customers; and health providers who have the knowledge to answer customer questions. The responsiveness dimension consisted of 4 statements, namely keeping customers informed about when services will be performed; prompt service to customers; willingness to help the customers; and readiness to respond to customers' requests. The empathy dimension consisted of 5 statements, namely giving customers individual attention without any discrimination; convenient business hours; health providers who understand the needs of their customers; having the customer's best interest at heart; and health providers who deal with customers in a caring fashion.[10] Each statement had two columns namely "expectation" and "reality" columns that had a score ranging from 1 to 10. Prior to data collection, the selected respondents were given explained about the purpose and procedure of the study. After they understood and agreed to participate in this study, they signed the informed consent form. The researcher read and explained the meaning of each statement one by one to the respondents and the respondents chose the right score for each statement both for the "expectation" and "reality" aspects.

The average score of the "expectation" and the "reality" was calculated by adding up the total score of "expectation" or "reality" divided by the number of samples. The satisfaction level was calculated by dividing the "reality" average score with the "expectation" average score and multiplied by 100%. Satisfied if the percentage reached ≥ 80%, and dissatisfied if the percentage was <80%.[11]

The collected data were statistically analyzed using Fisher's exact test or Kolmogorov-Smirnov test to identify the difference of satisfaction according to the characteristics of the respondents.

The importance and performance matrix had 2 components, those were the x-axis (performance/reality axis) and the y-axis
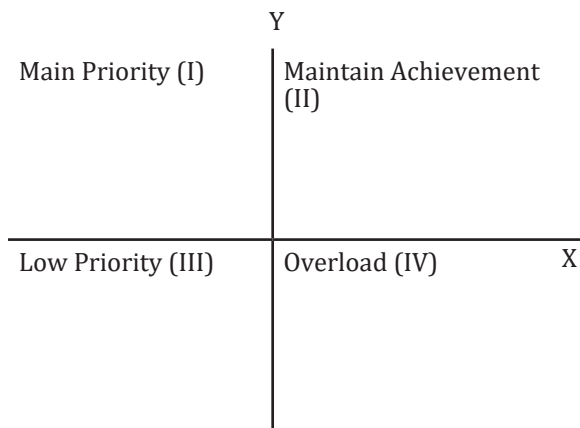
Y

Main Priority (I)	Maintain Achievement (II)
Low Priority (III)	Overload (IV) X

Figure 1 Importance-Performance Matrix

(importance/expectation axis).[12] The value of the x-axis was the "reality" average score and the value of the y-axis was the "expectation" average score.[12] This matrix created using IMB SPSS 22.0. Both axes create a Cartesian diagram that had four quadrants. (Figure 1).

Quadrant I showed customers feel that the health services provided by the *prolanis* was high, but the performance was low. The quality of health services that entered this quadrant should be prioritized to be improved because of the high importance and low satisfaction. Quadrant II showed the area in which health services at the *prolanis* needed to be maintained to make sure that the customers were still satisfied with the health services provided because the level of importance and performance were both high. Quadrant III showed a low priority area because of the low importance and low performance. The performance of the *prolanis* was low, and the importance perceived by the customer was also low. This situation did not mean that the organization did not have to enhance the quality of their services. They still had to provide health care better than before. Quadrant IV was categorized as overload area because there were factors that were not important for consumers (low importance level), but the organization provided the health care with a high performance.[12,13]

Results

The study on the satisfaction level of the elderly on the health care provided by the *prolanis* in Bandung City has been conducted using SERVQUAL questionnaires with total respondents of 112 elderly. Table 1 showed

Table 1 Respondent's Characteristics and Satisfaction

Characteristic	Frequency (n=112) (%)	Dissatisfied (n=9) (%)	Satisfied (n=103) (%)	p-value
Age (years old)				
60–69	70 (62.5)	3 (4.3)	67 (95.7)	0.078*
>70	42 (37.5)	6 (14.3)	36 (85.7)	
Education				
≤ Elementary School	44 (39.3)	3 (6.8)	41 (93.2)	
Junior high school	26 (23.2)	2 (7.7)	24 (92.3)	
Senior high school	27 (24.1)	1 (3.7)	26 (96.3)	0.831**
>Senior high school	15 (13.4)	3 (20.0)	12 (80.0)	
Marital status				
Not married	1 (0.9)	0 (0.0)	1 (100)	
Married	60 (53.6)	5 (8.3)	55 (91.7)	1.000**
Divorce	51 (45.5)	4 (7.8)	47 (92.2)	
Occupation				
Retired	88 (78.6)	6 (6.8)	82 (93.2)	0.400*
Employed	24 (21.4)	3 (12.5)	21 (87.5)	
Disease				
Hypertension	49 (43.8)	5 (10.2)	44 (89.4)	
Diabetes mellitus	34 (30.4)	0 (0.0)	34 (100)	0.889**
Hypertension and Diabetes mellitus	29 (25.9)	4 (13.8)	25 (86.2)	

Notes: *Fisher's exact test; ** Kolmogorov-Smirnov test

Table 2 Satisfaction Level

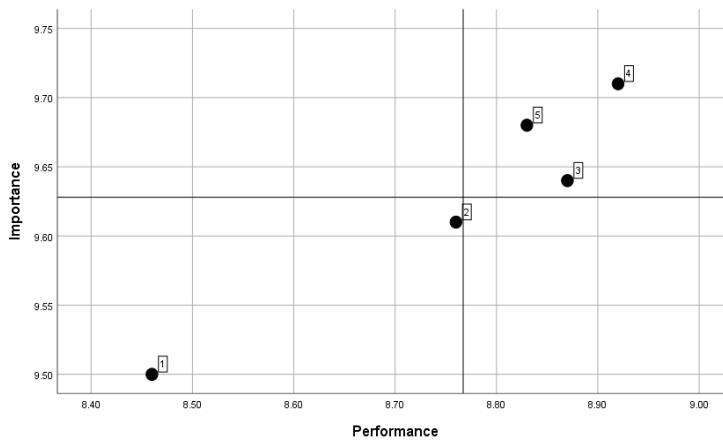| PKM	Total Satisfaction		Tangibles		Reliability		Responsiveness		Assurance		Empathy	
	Satisfy n (%)	Dissatisfy n (%)	Satisfy n (%)	Dissatisfy n (%)	Satisfy n (%)	Dissatisfy n (%)	Satisfy n (%)	Dissatisfy n (%)	Satisfy n (%)	Dissatisfy n (%)	Satisfy n (%)	Dissatisfy n (%)
PKM 1	36 (94.7)	2 (5.3)	37 (97.4)	1 (2.6)	35 (92.1)	3 (7.9)	37 (97.4)	1 (2.6)	37 (97.4)	1 (2.6)	38 (100)	0 (0.0)
PKM 2	5 (83.3)	1 (16.7)	0 (0.0)	6 (100)	1 (16.7)	5 (83.3)	6 (100)	0 (0.0)	6 (100)	0 (0.0)	6 (100)	0 (0.0)
PKM 3	8 (100)	0 (0.0)	8 (100)	0 (0.0)	8 (100)	0 (0.0)	8 (100)	0 (0.0)	8 (100)	0 (0.0)	8 (100)	0 (0.0)
PKM 4	11 (78.6)	3 (21.4)	11 (78.6)	3 (21.4)	11 (78.6)	3 (21.4)	12 (85.7)	2 (14.3)	10 (71.4)	4 (28.6)	13 (92.9)	1 (7.1)
PKM 5	16 (100)	0 (0.0)	15 (93.8)	1 (6.3)	16 (100)	0 (0.0)	16 (100)	0 (0.0)	15 (93.8)	1 (6.3)	16 (100)	0 (0.0)
PKM 6	7 (100)	0 (0.0)	6 (85.7)	1 (14.3)	7 (100)	0 (0.0)	7 (100)	0 (0.0)	7 (100)	0 (0.0)	6 (85.7)	1 (14.3)
PKM 7	10 (90.9)	1 (9.1)	10 (90.9)	1 (9.1)	10 (90.9)	1 (9.1)	10 (90.9)	1 (9.1)	10 (90.9)	1 (9.1)	10 (90.9)	1 (9.1)
PKM 8	10 (83.3)	2 (16.7)	10 (83.3)	2 (16.7)	11 (91.7)	1 (8.3)	10 (83.3)	2 (16.7)	12 (100)	0 (0.0)	6 (50)	6 (50)
Total	103 (92.0)	9 (8.0)	95 (84.8)	9 (8.0)	99 (88.4)	13 (11.6)	104 (92.9)	8 (7.1)	106 (94.6)	6 (5.4)	103 (92.0)	9 (8.0)

Note: PKM: puskesmas

Figure 2 Importance-Performance Matrix for 5 Dimensions of Satisfaction

Notes: 1. Tangibles; 2. Reliability; 3. Responsiveness; 4. Assurance; 5.Empathy

that most of the respondents were aged 60-69 years old, low education, married, retired, and had hypertension. There was no difference in satisfaction level satisfaction for all characteristic variables (p-value ≥0.05).

This study discovered that the satisfaction level was very high. The dimension that had the highest satisfaction level was the assurance dimension (94,6%) and the lowest was the tangibles dimension (84,8%; Table 2).

This study revealed that there were differences in the total satisfaction and in every dimension that existed in the eight *puskesmas*. In the *puskesmas* number 2, the total satisfaction was high, but in the tangibles and reliability dimensions, the satisfaction was low. *Puskesmas* number 4 had the lowest

level of satisfaction compared to the other *puskesmas* (Table 2).

This study discovered that tangibles and reliability dimensions placed inside the quadrant III, which means that both dimensions had a low priority to be improved, while assurance, responsiveness, and empathy dimensions placed inside the quadrant II which means the health providers needed to maintain the health service quality in these three dimensions (Figure 2).

Every statement in every dimension was plotted also into the Importance-Performance Matrix. This study discovered that "the complete medical equipment" statement (tangibles) placed in the first quadrant. Moreover, the "simple procedures" statement
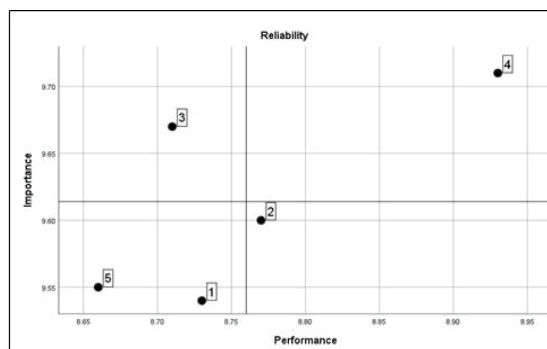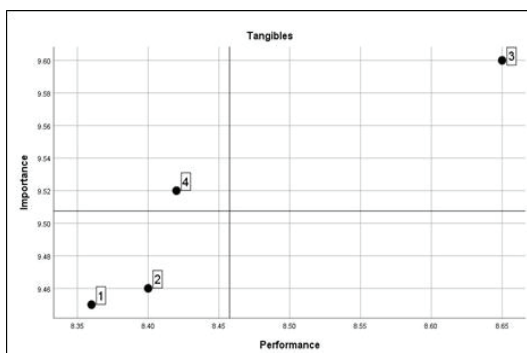
1.visually appealing rooms; 2. complete facilities;
3.employees who have a neat, professional appearance;
4.complete medical equipment

1.providing services as promised; 2.dependability in handling customers' problems; 3.simple procedures; 4.providing services at the promised time; 5.prompt administrative services.

Figure 3 Tangibles and Reliability Importance-Performance Matrix

1.health providers who instill confidence in customers;
2. making customers feel safe; 3. respect the customers; 4. health providers who have the knowledge to answer customer questions

1.keeping customers informed about when services will be performed; 2.prompt service to customers; 3.willingness to help the customers; 4.readiness to respond to customers' requests

1. giving customers individual attention without any discrimination; 2. convenient business hours; 3. health providers who understand the needs of their customers; 4. having the customer's best interest at heart; 5. health providers who deal with customers in a caring fashion
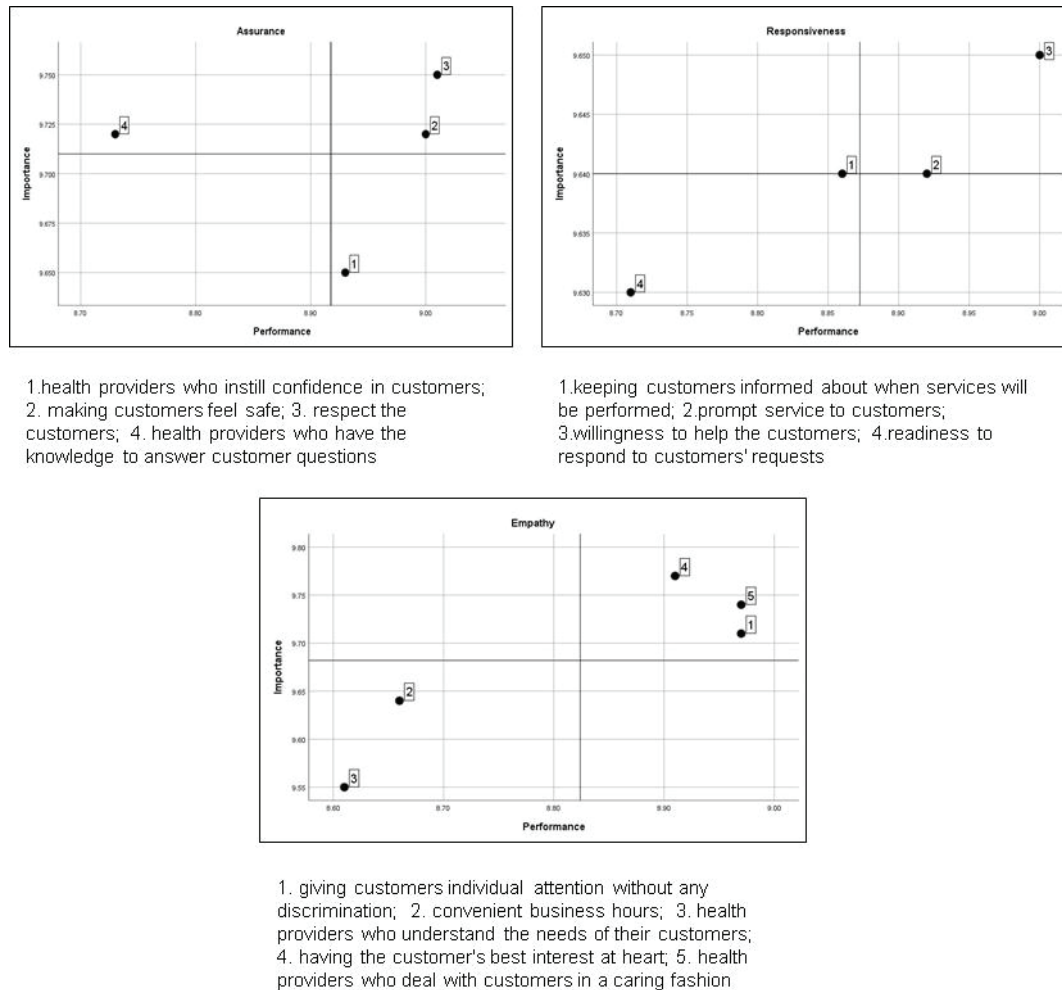
Figure 4 Assurance, Responsiveness, and Empathy Importance-Performance Matrix

(reliability) placed in the first quadrant as well (Figure 3).

Regarding the assurance dimension, this study discovered that the statement about "health providers who knew to answer customer questions" placed in the first quadrant (Figure 4).

Discussion

Prolanis is a health service system that involves patients, as members of the JKN, primary health facilities, and The Indonesian Social Security Agency in the health sector, who suffer from chronic diseases, especially hypertension and diabetes mellitus. Six *prolanis* activities consist of: (1) medical consultation; (2) health education; (3) SMS gateway reminder; (4) home visit; (5) physical exercise (gymnastics) and;

(6) monitoring health status.[3] The goal of the *prolanis* is to encourage participants to come to the *puskesmas* for monitoring and treating their diseases so that they achieve optimal quality of life and prevent complications.[3]

Patient satisfaction is one of the indicators for measuring the quality of health care services. Measuring the level of satisfaction is very important as satisfaction might affect adherence to treatment for chronic diseases such as hypertension and diabetes mellitus.[14] Moreover, assessing the level of satisfaction can give information on whether the services provided by the *puskesmas* are in accordance with the customer expectation.[6] This study discovered that most of the respondents were satisfied with the health services provided at the *prolanis* in every dimension, however, the tangible dimension had the lowest satisfaction

level compared to the other dimensions of SERVQUAL. Moreover, the responsiveness, assurance, and empathy dimensions placed in the Quadrant II of the importance-performance matrix which means that the quality of those dimensions should be maintained.[12,13]

From the tangible dimension, the main component that needed to be improved is the availability of medical equipment such as the insulin syringe. In Indonesia, hypertension and diabetes mellitus are chronic diseases that have become the primary concern for the public health sector.[15] The hypertension prevalence in Indonesia is quite high as many as 8.6–10%[16], while the diabetes prevalence is as many as 4,6%.[17] The management of hypertension and diabetes without complications is the authority of doctors who work at the *puskesmas*, therefore the availability of medicines and insulin syringes need to be considered.

The reliability dimension placed inside the quadrant III of the importance-performance matrix which means that this dimension had a low priority to be improved, however, there is one component of the reliability dimension that should be improved, namely the procedures at the *prolanis* was complicated, not a simple one, especially when the *puskesmas* referred them to the hospital. This is in accordance with the study by Nurheda et al., that the respondents were not satisfied because they had not been served promptly and tended to be convoluted.[18]

The ability of the health providers to answer the patients' questions is a component of the assurance dimension placed in the quadrant I. A study conducted by Andrew H. Van de Ven et al discovered that patients will feel satisfied if the health providers were able to explain about the condition of illness, the treatment given and the side effects of the medicine given to the patients.[19]

This study discovered that tangible and reliability dimension, and several components in other dimensions placed inside the quadrant III. This quadrant described that the respondents had a low expectation and the performance of the health care provided at the *prolanis* was low.[13]the purpose of this paper is to measure service quality provided to surgical and medical inpatients at Kerman Medical Sciences University (KUMS Compared to other quadrant, dimensions or statements placed in this quadrant showed a low priority to be intervened.[12,13] Sanam Roder-DeWan et al. stated that the low expectation of the patients, made them feel satisfied with the low quality of the health services. There was no demand to improve the quality of the health services and in the end the health providers will not make efforts to enhance the quality of their health services.[20]

This study has some limitations. This study did not link the satisfaction level with treatment adherence. There were lots of statements in the SERVQUAL questionnaire that require a considerable amount of time to answer by the respondents. This causes some of the elderly were suspected of not answering them in accordance with their choices.

The conclusion of this study is the satisfaction level of the elderly on the health care provided at the *prolanis* is high. The dimension with the highest satisfaction level is the assurance dimension (94,6%) and the lowest in the tangibles dimension (84,8%). The responsiveness, assurance, and empathy dimensions should be maintained so that the elderly satisfied with the health care provided, however, some of the components of tangible and reliability dimensions should be improved. Further study needed to be conducted to analyze the relationship between satisfaction level and the treatment adherence of patients with hypertension and diabetes.

References

1. BPS-Statistics Indonesia. Statistik penduduk lanjut usia 2019. Jakarta; 2019.
2. Indonesian Ministry of Health. Riset kesehatan dasar 2018. Jakarta: Badan Penelitian dan Pengembangan Kesehatan Kemenkes RI; 2018.
3. Rosdiana AI. Implementasi program pengelolaan penyakit kronis (Prolanis). Higeia J Public Heal Res Dev. 2017;1(3):140–50.
4. Asfiani LV, Ilyas Y. Level of adherence and its determinants of Prolanis attendance in type 2 Diabetes Mellitus participants at five BPJS primary health care in Bekasi 2016. J Indones Heal Policy Adm. 2017;2(2):6–13.
5. Raraswati A, Heryaman H, Soetedjo NNM. Peran program Prolanis dalam penurunan kadar gula darah puasa pada pasien Diabetes Melitus tipe 2 di Puskesmas Kecamatan Jatinangor. J Sist Kesehat. 2018;4(2):65–70.
6. Xesfingi S, Vozikis A. Patient satisfaction with the healthcare system: Assessing the impact

of socio-economic and healthcare provision factors. BMC Health Serv Res. 2016;16(1):1–7.

7. Sari DP, Harmawan A. Usulan perbaikan kualitas pelayanan pada instalasi rawat jalan dengan metode SERVQUAL dan TRIZ. J Tek Ind. 2012;95–6.

8. Rinnasa P-A, Nababan ESM, Bu'ulolo F. Strategi peningkatan kualitas pelayanan kesehatan menggunakan integrasi metode Fuzzy Servqual. Saintia Mat. 2013;1(6):529–41.

9. Oktavia D. Gambaran tingkat kepuasan dan harapan pasien pada pelayanan program pengelolaan penyakit kronis (PROLANIS) di wilayah kerja Puskesmas Kalimanah Purbalingga. [Thesis]; 2018.

10. Rinawan FR, Djuhaeni H, Arisanti N, Gondodiputro S, Pudjisetiawati E, Wiwaha G, et al. Kajian kepuasan pasien terhadap kualitas layanan PPK Primer Kota Bandung. Bandung: Dinas Kesehatan Kota Bandung; 2011.

11. Rajbanshi L, Dungana G, Gurung Y, Koirala D. Satisfaction with health care services of out patient department at Chitwan Medical College Teaching Hospital, Nepal. J Chitwan Med Coll. 2014;4(7):11–2.

12. Gonçalves JR, Pinto A, Batista MJ, Pereira AC, Bovi Ambrosano GM. Importance-performance analysis: Revisiting a tool for the evaluation of clinical services. SciRes. 2014;06(05):285–91.

13. Izadi A, Jahani Y, Rafiei S, Masoud A, Vali L. Evaluating health service quality: using importance performance analysis. Int J Health Care Qual Assur. 2017;30(7):1–9.

14. Bakar ZA, Fahrni ML, Khan TM. Patient satisfaction and medication adherence assessment amongst patients at the diabetes medication therapy adherence clinic. Diabetes Metab Syndr Clin Res Rev. 2016;10(2):1–17.

15. Dyanneza F, Tamtomo DS. The Effectiveness of chronic disease management program in blood pressure control among hypertensive patients. Indones J Med. 2017;2(1):52–62.

16. Syahrini EN, Susanto HS, Udiyono A. Faktor-faktor risiko hipertensi primer di Puskesmas Tlogosari Kulon Kota Semarang. J Kesehat Masy. 2012;1(2):315–25.

17. Mihardja L, Soetrisno U, Soegondo S. Prevalence and clinical profile of diabetes mellitus in productive aged urban Indonesians. J Diabetes Investig. 2014;5(5):507–12.

18. Nurheda, Usman, Rusman ADP. Hubungan kualitas pelayanan kesehatan dengan kepuasan pasien pengguna Badan Penyelenggara Jaminan Sosial (BPJS) di Puskesmas Maiwa Kabupaten Enrekang. J Ilm Mns dan Kesehat. 2018;1(3):201–16.

19. Van de Ven AH. What matters most to patients? Participative provider care and staff courtesy. Patient Exp J. 2014;1(1):131–9.

20. Roder-DeWan S, Gage AD, Hirschhorn LR, Twum-Danso NAY, Liljestrand J, Asante-Shongwe K, et al. Expectations of healthcare quality: A cross-sectional study of internet users in 12 low- and middle-income countries. PLOS Med. 2019;16(8):e1002879.

Comparison of Cognitive Functions between Paroxysmal and Persistent Atrial Fibrillation Patients without Clinical Stroke

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Abstract

Objective: To compare cognitive functions between paroxysmal and persistent atrial fibrillation patients without clinical stroke, in terms of MoCA-Ina total score and MoCA-Ina cognitive subdomains scores.

Methods: A comparative study that compared MoCA-Ina scores between paroxysmal and persistent AF patients without clinical stroke, who came for treatment at the Cardiology Clinic Dr. Hasan Sadikin General Hospital, Bandung and Dustira Hospital, Cimahi from September 2018–January 2019.

Results: Sixty four subjects were recruited, consisted of 24 paroxysmal and 40 persistent AF patients. There were no difference in clinical characteristics between two groups, except that there were more subjects in the persistent AF group using anticoagulants therapy: 97.5% vs 62.5% (p=0.005) and more prevalence of type 2 Diabetes Mellitus in the paroxysmal AF group: 25% vs 2.5% (p=0.009). Cognitive impairment (MoCA-Ina score <25) were seen in 70.8% of paroxysmal AF group and 82.5% of persistent AF group (p=0.274). The mean MoCA-Ina total score in the paroxysmal and persistent AF groups were 21.04±4.75 vs 20.70±4.21 (p=0.989), respectively. The median MoCA-Ina cognitive subdomains scores were similar for the two groups (p>0.05).

Conclusion: There were no differences in cognitive functions between paroxysmal and persistent AF patients, both in terms of MoCA-Ina total score and MoCA-Ina cognitive subdomains scores, although in both groups had cognitive decline.

Keywords: Atrial fibrillation, cognitive impairment, MoCA-Ina, paroxysmal AF, persistent AF

Introduction

Many studies have reported a significant association between atrial fibrillation (AF) and cognitive impairment and a faster incidence of dementia, both with and without the occurrence of clinical stroke that preceded it.[1,2] The prevalence of mild cognitive impairment (MCI) and dementia in AF patients was estimated at 40%, higher than patients without AF.[2,3]

The mechanism of cognitive impairment in AF patients is mostly related to the incidence of cardioembolic stroke, but it is well known that without a stroke, AF also can cause cognitive impairment. Although the mechanisms that play a role in this case are not fully understood, several hypotheses have been stated i.e the occurrence of the silent cerebral infarct (SCI), cerebral hypoperfusion, vascular inflammation and processes involving small vessels (small vessel disease/SVD).[3-5]

Paroxysmal and persistent AF are thought to have different pathophysiology of thrombus formation. Some experts argue that the short

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duration of AF in paroxysmal AF patients is associated with smaller and newly formed thrombus so that early recanalization is easier. In the contrary, thrombus in the persistent AF may be larger due to the larger size of the left atrial auriculum. Besides that the thrombus in persistent AF is more organized and stronger so that it tends to respond less to early recanalization. In addition, persistent AF is also associated with a greater number of lesions than paroxysmal AF. Therefore, persistent AF is considered more associated with a higher incidence of SCI and lower cognitive function as compared to paroxysmal AF, even without previous stroke events.[6]

The MoCA-Ina test (Indonesian version of Montreal Cognitive Assessment) is one of the most frequently used and validated test for cognitive impairment screening.[7] This test has a higher sensitivity and specificity in diagnosing mild cognitive disorders compared to the MMSE (Mini Mental State Examination) test because it covers all cognitive domains including executive functions.[8]

This study was aimed to compare cognitive function between paroxysmal and persistent AF patients without a clinical stroke, in terms of MoCA-Ina total score and MoCA-Ina cognitive subdomains score.

Methods

This was a comparative study of adult patients (age >18 years) with paroxysmal and persistent AF in the cardiology clinic at Hasan Sadikin Hospital Bandung and Dustira Hospital Cimahi. Patients were excluded if they have had one of the following: a history of clinical stroke, diagnosed as Rheumatic Heart Disease (RHD), a history of central nervous system abnormalities (i.e epilepsy, Parkinson's Disease, Multiple Sclerosis, moderate to severe head injury or brain infections), a history of systemic abnormalities (i.e moderate to severe congestive heart failure, chronic kidney disease, routine hemodialysis or HIV-AIDS), using memory enhancer or other psychopharmaceutical drugs and had a severe impaired vision, hearing and motor function that hampered the examination.

Ethical approval from the Health Research Ethics Committee of the Dr. Hasan Sadikin General Hospital Bandung under the ethical clearance No. LB.04.01/A05/EC/273/IX/2018 was gained prior the study. Sampling was conducted consecutively from September 2018 to January 2019. A comprehensive range of sociodemographic and clinical data were collected through questionnaires. Cognitive function data was obtained through the MoCA-Ina test. The elegible subjects were examined with MoCA-Ina test after signing the informed consent. The MoCA-Ina test was performed by a trained neurology resident. MoCA-Ina total score and MoCA-Ina cognitive subdomains scores were compared between the two AF groups. The research datas are described using tables according to the variables identified during the study. Data was analyzed using SPSS version 24.0 for Windows. The probability value $p<0.05$ is considered statistically significant.

Results

Sixty four subjects were recruited during the study's period, consisted of 24 paroxysmal and 40 persistent AF patients. The comparison of the basic characteristics of the subjects between the two AF groups was shown on Table 1. There were no significant differences in demographic characteristics (age, gender and education level) between the two AF groups, so that both of groups could be considered homogeneous and could be compared. From the clinical characteristics there were also no statistically significant difference, except for the history of taking anticoagulant therapy and the presence of type 2 DM variables, where there were more subjects in the persistent AF group who used anticoagulant therapy i.e. 97.5% vs 62.5% (p=0.005) and more comorbidities of type 2 DM in the paroxysmal AF group of 25% vs 2.5% (p=0.009). Both of these variables may act as confounding variables which can influence further statistical analysis.

The comparison of the results of the MoCA-Ina test of the subjects between the two AF groups was shown on Table 2. Cognitive impairment (MoCA-Ina total score <25) were found in paroxysmal and persistent AF groups (82.50% vs 70.80%, p=0.274). Similarly, the MoCA-Ina total score was decrease in the both AF groups with a mean of 21.04±4.75 vs 20.70±4.27 (p=0.989), respectively for the paroxysmal and persistent AF groups.

MoCA-Ina cognitive subdomain score were low in both groups, especially the executive functioning and memory, but did not show a statistically significant difference. (Table 2). Domains that were mostly disturbed in the paroxysmal AF group were the executive functioning (95.8%), memory (87.5%) and language (79.2%), while in the persistent AF group were memory (95%), executive

Table 1 Subject Characteristics

Variable	Group		p–value
	Paroxysmal AF (n=24)	Persistent AF (n=40)	
Age (years) Mean±SD	61.32±11.45	60.12±9.59	0.655
Gender			0.594
Male	8 (33.30%)	16 (40.00%)	
Female	16 (66.70%)	24 (60.00%)	
Education (years)			0.412
Median	9.00	9.00	
Range (min–max)	6.00–16.00	6.00–16.00	
Occupation			1.000
Active	23 (95.80%)	38 (95.00%)	
Not active	1(4.20%)	2 (5.00%)	
Duration of AF (years)			0.237
Median	2.25	4.00	
Range (min–max)	0.02–20.00	0.08–21.00	
Antiarrhythmic therapy			0.627
Yes	22 (91.70%)	38 (95.00%	
No	2 (8.30%)	2 (5.00%)	
Anticoagulant therapy	12 (50.00%)	38 (95.00%)	0.005*
Warfarin	3 (12.50%)	1 (2.50%)	
NOAC	9 (37.50%)	1 (2.50%)	
None			
INR value	21(87.50%)	24 (60.00%)	0.207
<2	3 (12.50%)	10 (25.00%)	
2–3	0 (0.00%)	6 (15.00%)	
>3	0	6	
Comorbidities			
Hypertension	16 (66.70%)	19 (47.50%)	0.136
Type 2 DM	6 (25.00%)	1 (2.50%)	0.009*
Ischemic Heart Disease	12 (50.00%)	12 (30.00%)	0.110
Heart Failure	12 (50.00%)	28 (70.00%)	0.110
CHA_2DS_2–VASc scores			
Median	3.00	3.00	0.068
Range (min–max)	1.00–6.00	0.00–5.00	

Note: *statistically significant, SD: standard deviation, min: minimal, max: maximal, AF: atrial fibrillation, NOAC: non vitamin K–antagonist oral anticoagulant, INR: International Normalized Ratio, DM: diabetes mellitus, CHA_2DS_2–VASc: Congestive heart failure, hypertension, Age ≥75 years, diabetes, stroke, vascular disease, Age ≥65 years, Sex category–female

functioning (90%) and attention (82.5%). Orientation domain was less disturbed in both groups. (Table 2)

Discussion

In this study, cognitive impairment in AF patients was prominent, as shown by the high proportion of low MoCA-Ina total score and its cognitive subdomain score. The average MoCA-Ina total score in this study was lower than the average MoCA total score for the normal population with the same age (23.20 ± 3.96).[9] The proportion of cognitive impairment in this study were almost the same with one study in Indonesia, that was 86.70%, with mean MoCA-Ina total score was 21.77±2.87.[10] Deficits in executive functioning and memory

Table 2 Results of MoCA–Ina Test

Variable	Group		p–value
	Paroxysmal AF (n=24)	Persistent AF (n=40)	
Cognitive decline based on MoCA–Ina score			0.274
≥25	7 (29.20%)	7 (17.50%)	
<25	17 (70.80%)	33 (82.50%)	
MoCA–Ina total score			
Mean±SD	21.04±4.75	20.70±4.27	0.989
Attention domain			
Median score	4.00	4.00	0.938
Range (min–max)	2.00–6.00	0.00–6.00	
Normal	6 (25.0%)	7 (17.5%)	
Abnormal	18 (75.0%)	33 (82.5%)	0.470
Memory domain			
Median score	2.00	2.00	0.943
Range (min–max)	0.00–5.00	0.00–5.00	
Normal	3 (12.5%)	2 (5.0%)	
Abnormal	21 (87.5%)	38 (95.0%)	0.355
Language domain			
Median score	4.00	4.00	0.842
Range (min–max)	1.00–6.00	2.00–6.00	
Normal	5 (20.8%)	9 (22.5%)	
Abnormal	19 (79.2%)	31 (77.5%)	0.876
Visuospatial domain			
Median score	3.00	3.00	0.825
Range (min–max)	2.00–4.00	2.00–4.00	
Normal	9 (37.5%)	15 (37.5%)	
Abnormal	15 (62.5%)	25 (62.5%)	1.000
Executive functioning domain			
Median score	1.00	1.00	0.611
Range (min–max)	0.00–4.00	0.00–4.00	
Normal	1 (4.2%)	4 (10.0%)	
Abnormal	23 (95.8%)	36 (90.0%)	0.642
Orientation domain			
Median score	6.00	6.00	0.993
Range (min–max)	3.00–6.00	2.00–6.00	
Normal	16(66.7%)	27(67.5%)	
Abnormal	8(33.3%)	13(32.5%)	0.945

Note: SD: Standard Deviation, min: minimal, max: maximal, MoCA–Ina: Indonesian version of *Montreal Cognitive Assesment*, AF: Atrial Fibrillation

were common, as were overlapping deficits across multiple cognitive subdomains.[11]

In– this study there was no statistically significant difference in cognitive function between paroxysmal and persistent AF patients. This condition was also failed to be shown in some previous studies, although some clinical parameters showed differences between the two groups.[12,13] On the contrary, several previous studies had found significant differences in cognitive function between patients with paroxysmal and persistent AF, but with different cognitive examinations.[6,14,15]

These different results might be causes

by several things i.e differences in the characteristics of the subjects, differences in the methodology, differences in cognitive function tests and differences in other comorbidities that can also affect cognitive function. In this study, between the two AF groups there were significant differences in two variables of clinical characteristics i.e the anticoagulant therapy and comorbidity of type 2 DM (Table 1). These two variables in the paroxysmal AF group could cause more severe cognitive impairment than they should be.

The majority of subjects in this study, especially the paroxysmal AF group, received less anticoagulant therapy and did not achieved therapeutic INR range so that they were at high risk for thromboembolism, including microemboli which could cause microinfarct in the brain, leading a cognitive impairment. This was in accordance with several previous studies, who stated that anticoagulant therapy and therapeutic INR were important to prevent embolism.[16,17] Futhermore, there was more comorbidity of type 2 DM in the paroxysmal AF group, where as it was known that AF patients who had type 2 DM comorbidity would have a higher tendency for cerebral ischemic which of course will have a negative impact on cognitive function, as showed in some previous studies.[18,19]

However, subsequent analysis of these two variables, both with multiple regressions (with adjusted) and other subanalysis, showed that there were no significant effects of these two variables on the analysis of the comparison of MoCA-Ina scores between the paroxysmal and persistent AF groups, even though the characteristics of the two variables significantly different between the two groups. One reason that can be considered is whether there are differences in the characteristics of anticoagulant therapy and comorbidity of type 2 DM variables which have not been further evaluated in this study such as the small number of samples with type 2 DM comorbidity, the effect of type 2 DM treatment and glycemic control, duration of drug use, compliance, the type of drug, the effectiveness and drug interactions that might be different in the two AF groups thus affecting the results of this study.

The results of several additional analyses above, most likely indeed illustrate that in this study most patients in the paroxysmal AF group had cognitive decline as well as in the persistent AF group. Although not in line with the differences in the pathophysiology of thrombus formation described previously, this is still possible because both groups have a median CHA_2DS_2-VASc score =3 which means that they have a high risk of thromboembolism/ microembolism as well as the risk of SCI. Several studies linking CHA_2DS_2-VASc scores with cognitive impairment, reported a 2-fold increased risk of cognitive decline in patients with a score of ≥3.[2,11] Nowadays screening and administration of anticoagulants in AF patients is not based on AF type but based on thromboembolic risk, one of which is using the CHA_2DS_2-VASc score.[20] Many guidelines have recommended the administration of anticoagulants for paroxysmal AF patients with the same criteria as those applied to persistent AF patients.[21]

By assuming that cognitive impairment is a predictor of SCI in paroxysmal AF patients, it is expected that different approaches can be given for the management of paroxysmal AF patients, such as periodic cognitive function screening, neuroimaging examination to see lesions of SCI and most importantly, early anticoagulant therapy can be given to the patients with impaired cognitive function even though the CHA_2DS_2-VASc score <2.

In addition to SCI, several other mechanisms need to be considered as the pathophysiology that causes cognitive impairment in AF patients, such as cerebral hypoperfusion and vascular inflammation.[4] However, there has been no studies that specifically analyzed them in paroxysmal and persistent AF patients. Furthermore, this study also did not collect and analyze variables that might be different in the two AF groups based on the above mechanisms, such as measurement of cardiac output or cardiac index which could be indicators of cerebral hypoperfusion or measurement of inflammatory mediators that could support the presence of vascular inflammation.

In conclusion, cognitive function in paroxysmal AF patients did not show differences with persistent AF patients in terms of MoCA-Ina total score and MoCA-Ina cognitive subdomain score. Both AF groups had lower cognitive function than the general population without AF. Therefore, it is important to screen cognitive function in all AF patients using the MoCA-Ina test, besides that it is necessary to consider giving anticoagulants for the prevention of stroke or SCI in AF patients.

References

1. Singh–Manoux A, Fayosse A, Sabia S, Canonico M, Bobak M, Elbaz A, *et al*. Atrial fibrillation as a risk factor for cognitive decline and dementia. Eur Heart J. 2017;38(34):2612–8.
2. Alonso A, Knopman DS, Gottesman RF, Soliman EZ, Shah AJ, O'Neal WT, *et al*. Correlates of dementia and mild cognitive impairment in patients with atrial fibrillation: the atherosclerosis risk in communities neurocognitive study (ARIC-NCS). J Am Heart Association. 2017;6(7):e006014.
3. Alonso A, de Larriva APA. Atrial fibrillation, cognitive decline and dementia. Eur Cardiol Rev. 2016;11(1):49–53.
4. Rivard L, Khairy P. Mechanisms, clinical significance, and prevention of cognitive impairment in patients with atrial fibrillation. Canadian J Cardiol. 2017;33(12):1556–64.
5. Kalantarian S, Ay H, Gollub RL, Lee H, Retzepi K, Mansour M, *et al*. Association between atrial fibrillation and silent cerebral infarctions: a systematic review and meta–analysis. Ann Intern Med. 2014;161(9):650–8.
6. Gaita F, Corsinovi L, Anselmino M, Raimondo C, Pianelli M, Toso E, *et al*. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. J Am College Cardiol 2013;62(21):1990–7.
7. Husein N, Lumempouw S, Ramli Y, Herqutanto. Montreal Cognitive Assessment versi Indonesia (MoCA–Ina) untuk skrining gangguan fungsi kognitif. Neurona. 2010;27(4):1–13.
8. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, *et al*. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695–9.
9. Rossetti HC, Lacritz LH, Cullum CM, Weiner MF. Normative data for the Montreal Cognitive Assessment (MoCA) in a population–based sample. Neurology. 2011;77(13):1272–5.
10. Salam S, Muis A, Aliah A, Akbar M, Kabo P, Jaya Ganda I. Hubungan Fibrilasi atrium dengan gangguan kognitif. 2014 April [cited 2018 January 14]. Available from: http://repository.unhas.ac.id/handle/123456789/9626.
11. Ball J, Carrington MJ, Stewart S, investigators S. Mild cognitive impairment in high–risk patients with chronic atrial fibrillation: a forgotten component of clinical management?. Heart. 2013;99(8):542–7.
12. Knecht S, Oelschläger C, Duning T, Lohmann H, Albers J, Stehling C, *et al*. Atrial fibrillation in stroke–free patients is associated with memory impairment and hippocampal atrophy. European heart journal. 2008;29(17):2125–32.
13. Gardarsdottir M, Sigurdsson S, Aspelund T, Rokita H, Launer LJ, Gudnason V, *et al*. Atrial fibrillation is associated with decreased total cerebral blood flow and brain perfusion. Ep Europace. 2018;20(8):1252–8.
14. Rozzini R, Sabatini T, Trabucchi M. Chronic atrial fibrillation and low cognitive function. Stroke. 1999;30(1):190–1.
15. Chen LY, Agarwal SK, Norby FL, Gottesman RF, Loehr LR, Soliman EZ, *et al*. Persistent but not paroxysmal atrial fibrillation is independently associated with lower cognitive function: ARIC Study. J Am College Cardiol. 2016;67(11):1379–80.
16. Jacobs V, Woller SC, Stevens S, May HT, Bair TL, Anderson JL, *et al*. Time outside of therapeutic range in atrial fibrillation patients is associated with long–term risk of dementia. Heart Rhythm. 2014;11(12):2206–13.
17. Demir S, Ozdag MF, Kendirli MT, Togrol RE. What Do Anticoagulants Say about Microemboli?. J Stroke Cerebrovascular Dis. 2015;24(11):2474–7.
18. Marseglia A, Fratiglioni L, Kalpouzos G, Wang R, Bäckman L, Xu W. Prediabetes and diabetes accelerate cognitive decline and predict microvascular lesions: A population–based cohort study. Alzheimers Dement. 2019;15(1):25–33.
19. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. J Diabetes Investig. 2013;4(6):640–50.
20. Jia X, Levine GN, Birnbaum Y. The CHA2DS2–VASc score: Not as simple as it seems. Int J Cardiol. 2018;257:92–6.
21. Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. Lancet. 2016;388(10046):806–17.

Relationship between the Quality of Informed Consent at Surgical Procedure in Terms of Ethics and Medicolegal with Satisfaction of Patient Health Service in dr. Zainoel Abidin Hospital

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Abstract

Objective: To determine the relationship between the quality of informed consent in terms of ethics and medicolegal with patient health service satisfaction at the dr. Zainoel Abidin Hospital (ZAH) Banda Aceh.

Methods: This study is an observational analytic with a cross-sectional method. Subject selection through a total sampling method. This study involved patients who were treated at dr. Zainoel Abidin Hospital (ZAH) Banda Aceh and a total of patients were 100 (52 men and 48 women) who met the inclusion criteria carried out on 16 December 2019 to 31 December 2019.

Results: As many as 90% of respondents rated informed consent made at ZAH as good quality and 85% expressed the satisfaction with health services at ZAH. An ethical and medicolegal review of informed consent emphasizes the basic principles of bioethics. As many as 84% of respondents stated that their autonomy rights had been fulfilled, 92.50% thought that the doctor had done beneficence, nonmaleficence, and justice well in the process of informed consent and 92.33% of respondents rated the three elements of informed consent as being well implemented. Based on the results of the chi-square statistical test showed a significant relationship between the quality of informed consent in terms of ethics and medicolegal with patient health service satisfaction under the value of p=0.001 (p≤0.05).

Conclusion: Good quality of informed consent in terms of ethics and medicolegal has an important role in increasing patient satisfaction with health services at the dr. Zainoel Abidin Hospital of Banda Aceh.

Keywords: Ethics, informed consent, medicolegal, satisfaction

Introduction

Informed consent (IC) consists of two words, namely informed which means that it has received an explanation or information, and consent means approval or giving permission.[1] IC is an embodiment of the patient-doctor relationship based on trust and good communication aimed at to get the best treatment results for patients. IC can be defined as the consent given by the patient and or his family to the doctor based on an explanation of the medical actions to be taken against the doctor and the risks associated by it.[2] IC is a method for sharing information between the doctor and the patient so it must occur collaboratively (cooperation) that both between doctors and patients and their families to get the best choice for the patient treatment.[3]

The patient-doctor relationship will be well established if each part understands the role itself and functions concerning IC. A

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doctor understands how to provide adequate information that can be accepted by patients. The doctor should provide information using language that is understood easily by patients. The doctor must also understand the sociocultural and emotional aspects of the patient.[4] The IC process does not only to get the patient's signature but rather respects the patient's right to autonomy.[5] IC while viewing through ethical principles is included in the basic rules of bioethics autonomy and when it views in the context of patient rights, IC is included in the right to self-determination.[6]

The quality of informed consent in terms of ethics can be assessed from the fulfillment of four basic principles of bioethics, that are beneficence, nonmaleficence, justice, and autonomy. Beneficence contains how the doctor will make informed consent which gives attention, friendliness, compassion, and empathy to patients. Nonmaleficence means that doctors try to minimize harm to patients with not to force it to frighten, and do not lie to patients in making decisions. Justice is genuinely done by doctors in conveying information and every patient is given an informed consent process before medical treatment. Autonomy is a right that is owned by the patient, namely how the patient gets information, giving choices, privacy, confidentiality and the right to give consent.[6,7,8]

Based on medicolegal, IC is a legal concept that guarantees the patients have the right to know about the risks, benefits and alternative therapies to be taken,[7] also if included in the approval of civil medical actions which if not implemented can be categorized as violating the law.[2,8] Quality of informed consent in terms of medicolegal can be assessed from fulfillment based on three aspects, namely, the approver must be competent that is aged 21 years or more (threshold element), the giver of explanation and the contents of the explanation (information element), and approval (consent element). This concentration element consists of two parts, namely, voluntariness (freedom) and authorization (authority).[8] The fundamental problem is that there are still many findings in the field about the informed consent process that have not been implemented properly so that it has the potential to be a problem of ethical and medicolegal violations. The ethical aspects related to IC focus on autonomy, trust, self-determination, personal integrity, and non-dominance. While the medicolegal aspect is protection, prevention of deviant behavior

and procedures that are not essential. IC is still often become a cause of conflicts between doctors and patients.[6,7,8]

From previous study reported that poor communication is the highest cause of patient complaints with prevalence in Jakarta 66,3%.[3] In Indonesia, obstacles in conducting ICs, including explanation problems which the patient does not understand. The results of the study of patient safety management team for hospital services obtained information that giving of informed consent in various health service institutions only asks patients to sign an informed consent sheet so that it affects the knowledge of patients and families.[9,10] The main of purpose this study was to determine the relationship between the quality of informed consent in terms of ethics and medicolegal at surgical procedures with the satisfaction of patient health services in Dr. Zainoel Abidin hospital (ZAH) of Banda Aceh.

Methods

This research is an observational analytic with a cross-sectional method. Subject selection through a total sampling method. This study involved patients who were treated at the Dr. Zainoel Abidin hospital of Banda Aceh numbered 100 people (52 men and 48 women) who met the inclusion criteria carried out on December 16, 2019, to December 31, 2019. This study has conducted ethical clearance and has been approved by the ethics committee of the health research, the Faculty of Medicine, Syiah Kula University / Zainoel Abidin Hospital No. 333/EA/FK-RSUDZA / 2019.

Inclusion criteria in this study include (1) male and female patients over the age of 21 years, (2) patients who have had surgery, (3) patients who have given informed consent before the treatment, (4) patients who can read and write and communicate well. Exclusion criteria: (1) patients suffering from mental disorders.

The data taken is the primary data. Primary data were obtained from the results of filling out the informed consent quality questionnaire to determine the quality of the informed consent in terms of ethical and medicolegal aspects, and also the satisfaction of patient to health services obtained from the results of filling out the questionnaire that had been tested for validity. The questionnaire used in this study was made by the research team and has been validated with a validity value> 0.361 and reliability 0.871.

Results

The study was conducted on patients treated in Raudhah rooms of ZAH as many as 100 respondents, with characteristics based on age and gender presented in table 1. The average value of participant age was 51.52 (SD 15.51), 50.50 median, 47 modus, 21 minimum, and 83 maximum.

Table 1 shows that based on gender, most respondents are male with 52 respondents (52%) and based on age group, most respondents aged between 56 to 65 years are 26 respondents (26%), although the mode of age of respondents is not from these group but from the age group of 46–55 years that is 47 years old respondents are 7 respondents (7%). In terms of age, all respondents have the right to give consent which is 21 years or older so that the threshold element is fulfilled 100%. All participants stated that the doctor who explained was the doctor who took the surgery, from this statement it could be concluded that there was fairness in treating respondents in the IC process (justice fulfilled 100%). The description of the quality of informed consent in terms of ethics and medicolegal is shown in table 2:

Table 2 shows that the basic rules of bioethics have been implemented well. As many as 84% of respondents stated that their autonomy rights had been fulfilled and on average 92.50% thought that the doctor had done beneficence, nonmaleficence, and justice well in the informed consent process. Medicolegal obtained an average of 92.33%

of respondents rated the three elements of informed consent as fulfilling the medicolegal rules. Accumulatively, the assessment of ethical and medicolegal aspects is carried out simultaneously, the fulfillment of the basic ethical principles of beneficence and nonmaleficence is assessed when the doctor provides information (information element), while the autonomy rules are assessed together with the consent element. From the tabulation obtained data about the quality of informed consent in the hospital room ZAH cumulatively percent shows that of 100 respondents regarding the quality of informed consent, 90 respondents rated good (met the ethical and medicolegal rules) and 10 respondents rated not good.

The level of patient satisfaction with health services in ZAH was assessed based on 5 aspects, there are tangibles, reliability, responsiveness, assurance, and empathy. Obtained an overview of the level of satisfaction of health services from each respondent as listed in Table 3.

Table 1 Characteristics of Respondents

Characteristics	Frequency of Respondents	
	(n=100)	%
Age		
21–25 years	8	8
26–35 years	14	14
36–45 years	12	12
46–55 years	20	20
56–65 years	26	26
>65 years	20	20
Gender		
Man	52	52
Women	48	48

Table 2 The Description of the Quality of Informed Consent in Terms of Ethics and Medicolegal

Rated Aspect	Assessment	
	Fulfill (%)	(%)
Ethics		
Beneficence	93 (93)	7 (7)
Non maleficence	93 (93)	7 (7)
Justice	100 (100)	0
Autonomy	84 (84)	16 (16)
Average	92,50 (92,50)	7,50 (7,50)
Medicolegal		
Threshold element	100 (100)	0
Information element	93(93)	7 (7)
Consent element	84 (84)	16 (16)
Average	92,33 (92,33)	7,67 (7,67)
IC Quality		
Ethics and medicolegal	90 (90)	10 (10)

Table 3 Overview of Patient Satisfaction with Service Quality based on the Five Dimensions of Service Quality

Service Satisfaction	Satisfied	%	Not Satisfied	%
Tangibles	96	96	4	4
Reliability	81	81	19	19
Responsiveness	86	86	14	14
Assurance	92	92	8	8
Emphaty	95	95	5	5
Over all of service satisfaction	85	85	15	15

Table 3 shows that from 100 respondents, most respondents expressed satisfaction with the reality (tangibles) and empathy in providing health services as much as 96 and 95 percent. From the tabulation obtained data about patient satisfaction with health services in the hospital room of ZAH cumulatively based on statistical calculations showed that out of 100 respondents, 85 respondents rated satisfaction with services in ZAH and 15 respondents rated dissatisfaction in service at ZAH. In this study to assess the relationship between the quality of informed consent in terms of ethical and medicolegal aspects with the satisfaction of health services, the Chi-Square statistical test is used in Table 4.

In this study, the Chi square test was used to determine the relationship or effect of two nominal variables and to measure the strength of the relationship between these variables. Based on Table 4 it can be explained that the results of the chi-square statistical test showed a significant relationship between the quality of informed consent in terms of ethics and medicolegal with patient health service satisfaction with a value of p=0.001 (p≤0.05).

Discussion

IC must make the patient understand in the context of receiving information before the patient gives consent for medical treatment against them, this can be achieved if there is effective doctor-patient communication.[3] Patient satisfaction is also related to the quality of IC. Patient satisfaction is always the main target of health services. Quality treatment results are indicators of the quality of health services.[5] Discussing patient satisfaction with health care, especially in surgical procedures and its relation to IC quality is not easy, because it is difficult to determine how the patient's understanding of surgical procedures.[1] Determination of patient satisfaction with health services is also not easy to achieve because of many factors that influence it, including socioeconomic, knowledge, culture, health status, doctor-patient relationship, staff performance, number of facilities, and medical records system.[5]

Regarding surgery, two principles of medical ethics are related closely, namely the principle of autonomy and non-maleficence. A patient must get full information before getting surgery and enough data must be submitted by the doctor to the patient so that ethical and medicolegal aspects can be accomplished.[2] The principle of autonomy means the doctor's moral principle to always respect the patient's rights, especially in this case is the right to

Table 4 The Relationship between the Quality of Informed Consent in Terms of Ethical and Medicolegal Aspects with the Satisfaction of Health Services

	Health Service Satisfaction			
	Satisfied	Not Satisfied	(n=100)	p-value
The Quality of Informed Consent				
Good	81	9	90	0,001*
Not Good	4	6	10	

determine what can be done to him (the right to self-determination), which is then developed in the doctrine of informed consent. The principle of non-maleficence is the moral principle of the doctor not to take actions that will worsen the patient's condition (primum non nocere, above all, do no harm).[8]

The results of this study conducted at the Raudhah ward (surgery ward) of ZAH in 100 respondents found a relationship between the quality of informed consent in terms of ethics and medicolegal with patient health service satisfaction. This is in line with a study conducted by Jhonson et al, in which result there was a significance relationship between giving informed consent and the level of satisfaction on the day of surgical procedure (p=0,02).[11] The results of this study were also supported by Sari's study showed that there was a relationship between giving informed consent before surgery and patient satisfaction.[12] When viewed specifically, the quality of Informed consent at ZAH most of the respondents rated good for both the giver of explanation, the contents of the explanation, and the giver of approval. Judging from the results of this study it was found that the doctors at ZAH had given good informed consent judged from ethical and medicolegal aspects.

During the interview with the respondent, the respondent also stated that the doctor who gave the IC was patient enough to wait for the patient's answer, allow to asking questions, and when giving consent there was no pressure and force. Thus the nonmaleficence code of ethics has also been implemented well which means that the doctor has tried to minimize losses to the patient due to decision making without coercion, fear or deception from the doctor. However, there are 7% of respondents who stated that there was a compulsion but not from a doctor but from a patient's family who wanted an immediate operation even though the patient himself did not want to. This research is different from research conducted by Aldossari et al.,[5] who found that 8.3% of respondents felt pressured by medical staff in decision making.

From an ethical perspective, in this study, there were still 16% of respondents who had not been accommodated in their autonomy rights. This shows that respondents and the Indonesian people, in general, are still not strong in autonomy because it is common knowledge that Indonesia is still communal, that is, everything is left to the family and not yet entirely dependent on independent

decisions. The right of autonomy that has not yet been fulfilled is privacy (freedom of choice) because it still depends on the family of 14% and the right to give consent of 2%. From the aspect of Justice, doctors have done well both when giving information and when getting patient approval, all done fairly.

IC is a process that shows effective communication between doctors and patients and the meeting of thoughts about what will and what will not be done to patients. IC viewed from the legal aspect is not as an agreement between two parties, but rather towards unilateral agreement on services offered by other parties. Viewed from civil law, the relationship between health care providers and health service recipients is a contractual relationship. From this relationship, a bind of agreement between the two parties arises and rights and obligations emerge from each side. What is the right of the first side will become an obligation for the other side, and vice versa.[7,8,13]

In medicolegal, IC has 3 elements, namely threshold elements, information elements, and consent elements. The threshold element, ie the consent giver must be competent. By law a person is considered competent (competent) is when an adult, conscious and in a mental state that is not under control. An adult is defined as an age that has reached 21 years or has ever been married.[13,14] Information elements, consisting of two parts, namely disclosure and understanding. In this study, doctors have provided adequate information (93%), but there are also 7% inadequate that is related not given information about the benefits of the actions taken (5%) and doctors do not introduce themselves when giving IC (2%). Understanding based on adequate understanding brings consequences to medical personnel to provide information (disclosure) in such a way that the patient can reach an adequate understanding. Many experts say that if this element is not done then the doctor is considered to have neglected to carry out his duty to provide adequate information.[7,8,13] Consent elements also consist of two parts, namely, voluntariness (freedom, freedom) and authorization (approval). Volunteering requires no deception, misrepresentation or coercion. Patients must also be free from "pressure" by medical personnel who behave as if to be "left" if they do not agree to the offer. Many experts still argue that carrying out "not excessive" persuasion can still be morally justified.[8,13]

The description of patient health service

satisfaction shows that of 100 respondents, 85 respondents rated satisfaction with the service and 15 respondents rated dissatisfaction. Following the research objective of knowing the level of satisfaction of Raudhah inpatients with services, the following discussion will be carried out the results of research on patient satisfaction in evaluating the quality of health services by applying the concept of "RATER" that is reliability, assurance (guarantee), reality (tangibles), empathy and responsibility.[14] According to Muninjaya[14] which states that satisfaction is defined as the recipient's service response to the suitability of the customer's interest level with real performance can be felt after the service user receives the service.

The suitability of IC quality with patient satisfaction with health services is reflected in what is delivered to the patient at the time of providing information following what the patient feels after the surgical procedure is performed.[6,7,8] This conformity is described: reliability criteria reflected by attitude the hospital staff who able to handles patient care issues precisely and professionally and who arrive on time to the room when the patient needs it, this is in accordance with the ethical principles of beneficence and non-maleficence. Hospital staff informs clearly them of the things that must be followed in treatment (autonomy and beneficence). Hospital staff notifies clearly about matters that are prohibited in treatment (autonomy and nonmaleficence).[7,8] Assurance criteria reflected by attitude the hospital staff who pays attention to complaints the patient feel, who can answer questions about the treatment actions given, who honest in providing information about the situation and who always gives greetings and smiles when meeting to the patient, this is in accordance with beneficence and autonomy. Tangibles criteria reflected by attitude the hospital staff who always maintains neatness and appearance (beneficence). Emphaty criteria reflected by attitude the hospital staff who gives information about all treatments that will be carried out (autonomy-beneficence), who attentives and provides moral support for the patients (beneficence), services

provided by hospital staff do not look at rank / status but are based on patients conditions (justice-autonomy), Responsiveness criteria reflected by attitude the hospital staff who are are willing to offer assistance to the patient when patient experience difficulties even without being asked (beneficence and non-maleficence).[6,7,8,13]

The results of the study on the level of patient satisfaction with health services in the Raudhah Room of ZAH showed that expressed satisfaction generally with the health services. Chi-Square statistical test results obtained p-value 0.001 in this study showed that there was a significant relationship between the quality of informed consent of surgical procedures in terms of ethics and medicolegal with patient health service satisfaction in ZAH ($p<0.05$). This shows that the quality of informed consent at ZAH which has been good also contributed to the level of patient satisfaction. The results of the study are supported by Hallock et al.[1] study which states there was a significant association between satisfaction and knowledge of informed consent. According to Sari's study, that the patient's health condition includes the diagnosis of the course of the disease, the process of medical treatment, and the results of services. Indicators of health services chosen by patients are priority measures of the quality of health services, tend to be the main source of the formation of patient satisfaction.[12]

This study shows that there is a relationship between the basic rules of bioethics applied to the IC process with patient satisfaction criteria. Good quality IC in terms of ethics and medicolegal have an important role in increasing patient satisfaction with health services at the Dr. Zainoel Abidin Hospital of Banda Aceh. A limitation of this study is that data collection is limited to respondents in the operating theater at the time of the study, so the results of the study may not reflect all patients who had undergone previous operations. It might also not be relevant to the experience of patients in other rooms. But in general, this study is very useful for the development of hospital service systems in the future.

References

1. Hallock JL, Rios R, Handa VL. Patient satisfaction and informed consent for surgery. Am J Obstet Gynecol. 2017;217(2): 181.e1-181.e7.

2. Akasha RA, Beshi L, El-Fadul M. Mapping the quality of informed consent for major surgeical prosedures in public dental hospital in Khartoum state, Sudan, 2017: a crross sectional study. Dentristy. 2018;8 (11):1–7.

3. Afandi D. Aspek medikolegal dan tata laksana persetujuan tindakan kedokteran. Jurnal Kesehatan Melayu. 2018;1(2):99–105.
4. Sukendar S, Rahim AH, Hutabarat S. Tanggung jawab rumah sakit atas kelengkapan informed consent pada saat operasi di RS Primier Jatinegara jakarta. Soepra Jurnal Hukum Kesehatan. 2016;2 (2):229–40.
5. Aldossari SH, Alfayed SS, Al Mutlaq RI, AlTurki DI, Aljaser AK, Nouh TA. The relationship between quality of informed consent and perioperative care, and patient satisfaction: a tertiary-care hospital's experience. International Journal of Medical and Health Research. 2017;3(9):107–12.
6. Beauchamp TL, Childress JF. Principles of Biomedical Ethics. 7th ed. New York: Oxford University Press. 2013. p. 190-317.
7. Shaha KK, Patra AP, Das S. The importance of informed consent in medicine. Sch J App Med Sci; 2013;1(5):455–63.
8. Sharma R. Informed consent in clinical practice and research: ethical and legal perspective. Int J Healthcare Biomed Res. 2014;3(1):144–151.
9. Realita F. Implementasi persetujuan tindakan medis (informed consent) pada kegiatan bakti sosial kesehatan di Rumah Sakit Islam Sultan Agung Semarang. Jurnal Involusi Kebidanan. 2014:4(7):25–39.
10. Kustiawan R, Lesharini E. Pengalaman pemberian informed consent tindakan pembedahan pada pasien pre operatif elektif di Ruang IIIA RSU Kota Tasikmalaya. Jurnal Kesehatan Bakti Tunas Husada. 2014;(11)1:68–77.
11. Johnson MR, Singh JH, Steaward T, Gioe TJ. Patient understanding and satisfaction in informed consent for total knee arthroplasty: a randomized study. Artritis Care Res. 2011;63(7):1048–54.
12. Sari PD. Hubungan antara pemberian informed consent sebelum tindakan operasi dengan kepuasan pasien. Jurnal INFOKES. 2016;6(2):1–4.
13. Patil AM, Anchinmane VT. Medicolegal aspects of consent in clinical practice. Bombay Hospital Journal. 2011;53(2)203–8.
14. Muninjaya G. Manajemen kesehatan. 3rd ed. Jakarta: Penerbit EGC; 2011.

Serum Albumin Levels of Oral Candidiasis Immunosuppressed Rats Treated with Hyperbaric Oxygen

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Abstract

Objective: To investigate serum albumin levels in oral candidiasis immunosuppressed rats treated with hyperbaric oxygen. One of the predisposing factors for oral candidiasis was the use of immunosuppressive drugs continuously. It can also affect the work of the liver because it's one of the organs responsible for drug metabolism. Hyperbaric oxygen therapy was used not only to suppressing fungal infections, but also to improve liver function by evaluating the serum albumin levels.

Methods: This study used a post-test only control group design. Fifteen Wistar rats were divided into 3 groups(n=5/3): G1 (healthy group), G2 (oral candidiasis immunosuppressed rats group without hyperbaric oxygen therapy), and G3 (oral candidiasis immunosuppressed rats group with hyperbaric oxygen therapy). G2 and G3 groups were immunosuppressed by giving dexamethasone 0,5mg/day/rat orally for 14 days, added with tetracycline 1 mg/day/rat. Hyperbaric oxygen therapy was given to the G3 group in 5 days. Blood serum of rats in all groups was taken to calculate albumin levels.

Results: The average value of albumin levels in G2 group showed a decrease compared to the G1 group, while G3 showed the highest level. One way Anova test showed a significant difference among groups (p<0,05). To compare the difference between each group we used LSD test and showed a significant difference (p<0,05) between G1 compared to G2, G1 compared to G3, and G2 compared to G3.

Conclusion: Liver albumin levels of oral candidiasis immunosuppressed rats treated with hyperbaric oxygen therapy showed higher levels than those without therapy**.**

Keywords: Albumin, hyperbaric oxygen, immunosuppressed, liver, oral candidiasis

Introduction

Oral candidiasis is a fungal infection that occurs in the oral cavity. The cause of this infection, as many as 95% of cases are *Candida albicans*.[1] One of the predisposing factors for this infection is the use of immunosuppressive drugs, which can enhance the growing colonies of *Candida albicans*.[2,3]

The liver is one of the organs in the body that liable for drug metabolism. Drugs contained in the blood will be absorbed through the hepatic entero circulation, which will then be metabolized in the liver.[4] In addition to being a predisposing factor for oral candidiasis, continuous use of immunosuppressive drugs can affect the function of hepatocytes as a major part of metabolic agents, which can subsequently cause liver injury.[4,5]

Any abnormalities in the liver can be identified using liver function tests, one of them by evaluating serum albumin. It also can provide information about liver function.[6,7] Changes in its levels more or less than normal, can be a sign of liver damage, and also determine the prognosis of liver disease. The levels of this serum albumin can be used as indicators in hepatocellular function. A decrease in albumin levels can indicate liver disease such as cirrhosis hepatis.[8]

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Hyperbaric oxygen therapy (HBOT) has been reported as one of the therapies that had a significant effect on suppressing fungal infections.[9,10] Previous study showed that hyperbaric oxygen therapy 2.4 ATA which was given 3x30 minutes/day for 5 days, could increase the number of lymphocytes in oral candidiasis immunosuppressed model. It could be used as one of the adjuvant therapy in eliminating oral candidiasis infections.[11] Hyperbaric oxygen therapy was also reported as therapy used in several liver diseases, such as acute liver injury, liver fibrosis, non-alcoholic steatohepatitis, cancer, and also has a beneficial effect on liver regeneration due to the antioxidant and anti-inflammatory effect derived from its mechanism.[12]

Based on the description above, the aim of this study was to investigate serum albumin levels of Wistar rats in oral candidiasis immunosuppressed condition which was treated with hyperbaric oxygen.

Methods

This study used a post-test only control group design. The population of this study was fifteen male Wistar strain rats, 6 months old, weighs 200–250 grams, and divided randomly into three groups: G1 (healthy rats group), G2 (oral candidiasis immunosuppressed rats group without hyperbaric oxygen therapy), and G3 (oral candidiasis immunosuppressed rats group treated with hyperbaric oxygen 2,4 ATA 3x30 minutes/day for 5 days). Immunosuppressed condition in rats was made by giving dexamethasone 0,5 mg/day and tetracycline 1 %/day orally. On the 4th day, we reduce the dose as much as 10% for dexamethasone and tetracycline, then rats were induced with *Candida albicans* (ATCC-10231) $6x10^8$ as much as 0,1 cc, applied on

Table 1 The Mean and Standart Deviation (SD) of Albumin Levels in Each Group

Groups	Albumin (g/dl) Mean±SD
G1 (healthy rats)	3.2±0.12
G2 (oral candidiasis immunosuppressed rats without HBOT)	2.96±0.17
G3 (oral candidiasis immunosuppressed rats with HBOT)	3.4±0.12

the dorsum tongue of rats using a sterile cotton bud, given once every two days for 12 days.[11,13]

Hyperbaric oxygen therapy was given to the G3 group for five days. During therapy with hyperbaric oxygen, rats were still given tetracycline 0,1 mg/day to prevent bacterial infection. The rats were placed in the mono-place chamber, the pressure was increased to 2,4 ATA, then pure oxygen (100%) was flowed for 3x30 minutes, with intervals breathing normal air for 5 minutes. After that, the pressure was lowered to the initial pressure (1 ATA).[11] The blood of rats in all groups was taken from their heart using a syringe, as much as ± 3cc, then centrifuged to obtain the blood serum for counting albumin levels.

Statistical analyses were done with the Lavene statistical test to perform the homogeneity of the data. We used a statistical one-way Anova test to show the different levels of serum albumin among groups, then the Post Hoc LSD test to show the significant difference among each group. To compare the serum albumin levels between groups that were given hyperbaric oxygen therapy and group which did not, we used an independent sample t-test.

This study was conducted in the oral biology laboratory of Dentistry Faculty Universitas Hang Tuah Surabaya, Faculty of Medicine Universitas Hang Tuah Surabaya, and Balai Besar Laboratorium Kesehatan Surabaya, which was held during August-December 2019. This study has been approved by Ethics Commission of Dentistry Faculty Universitas Hang Tuah Surabaya (No: EC/010/KEPK-FKGUHT/VII/2019).

Results

The mean value of serum albumin levels in the G2 group showed the lowest, compared to G1 and G3 group, while in G3 showed the highest mean value of serum albumin levels. We used the homogeneity of variances test using the Lavene statistic test and showed the homogeneous data (p>0.05). One way Anova test showed a significant difference among groups (p<0.05). LSD test was used to compare the difference between each group and showed significance value (p<0.05) between G1 compared to G2, G1 compared to G3, and G2 compared to G3. This means that there was a significant difference between G1 group compared to G2, between G1 compared to G3, and between G2 compared to G3. To ascertain the differences between groups of

Table 2 Serum Albumin Levels between Oral Candidiasis Immunosupressed (OCI) Rats Group with and without Hyperbaric Oxygen Therapy

Variable	OCI without HBOT	OCI with HBOT	p value
Serum Albumin (g/dl)	2.96±0.17	3.4±0.12	0.001*

p value was obtained from independent sample t-test

oral candidiasis immunosuppressed rats given hyperbaric oxygen therapy and those which did not, we used an independent sample t-test, and showed a significant difference between groups (sig.2 tailed <0,05).

Discussion

Serum albumin levels of oral candidiasis immunosuppressed rats treated with hyperbaric oxygen 2,4 ATA 3x30 minutes/ day with 5 minutes interval breathing in normal air, given for five days continuously (G3 group), showed the highest levels compared to the G1 and G2 groups. This elevation of serum albumin levels was in line with a previous study which showed that the administration of hyperbaric oxygen therapy could significantly increase serum albumin levels in patients with diabetic foot ulcers.[14] Several studies revealed
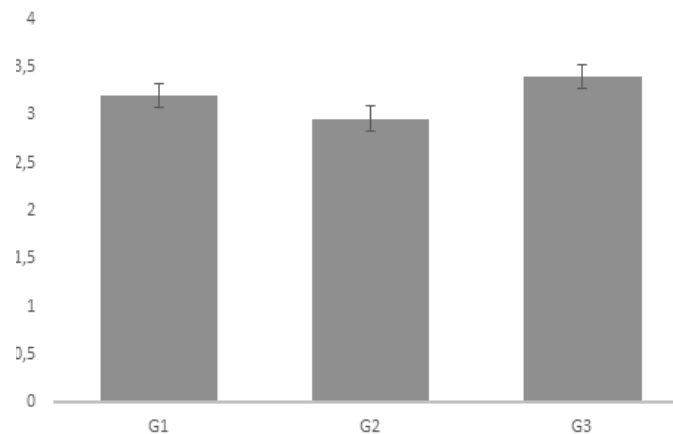

Fig. 1 Graphics of Average Value of Albumin Levels in Each Group. Healthy rats group (G1), Oral Candidiasis Immunosupressed (OCI) Rats Group without Hyperbaric Oxygen Therapy (G2), and Oral Candidiasis Immunosupressed (OCI) Rats Group Treated with Hyperbaric Oxygen 2,4 ATA 3x30 minutes/day for Five Days (G3)
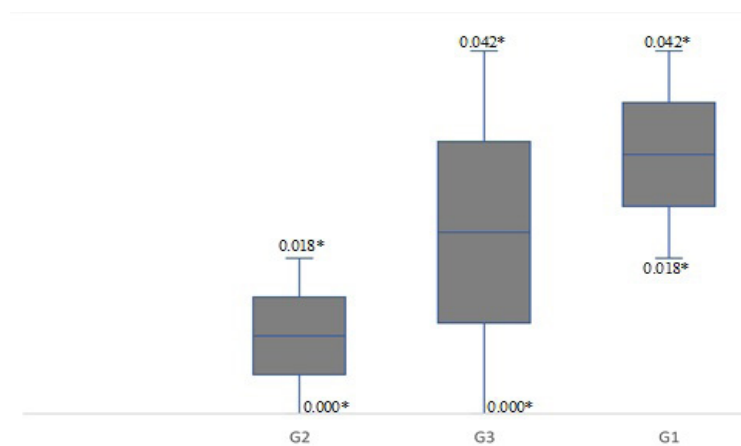

Fig. 2 Diagram of the Significance Value in Each Group Obtained from LSD Test
   ***significant difference (p<0.05)**

the effect of hyperbaric oxygen therapy on liver disease. This therapy could increase the proliferation of hepatocytes in liver injury, and preserved hepatocyte cells from necrosis on liver transplantation rats model.[12] This therapy also reported having a hepatoprotective effect in hepatocellular necrosis which was caused by excessive administration of acetaminophen in rats model.[18] Hyperbaric oxygen therapy could increase the level of dissolved oxygen transported to the tissues systemically,[14] moreover, oxygen transported to the injured liver will also increase.

Serum albumin is the most substantial plasma protein in the body, about 50% of the total protein, which is mainly synthesized in the liver. Albumin acts as the main modulator in the distribution of fluids throughout the body's space. Some of the albumin functions are maintaining colloid oncotic pressure in plasma and interstitial fluid, responsible for water retention, as an antioxidant and anti-inflammatory, and also in endothelial protection.[8,15] Treatment using albumin, is currently become one of the choices in the treatment of liver disease, especially in liver cirrhosis.[8]

Based on the results of this study, serum albumin levels of oral candidiasis immunosuppressed rats without hyperbaric oxygen therapy (G2) showed a decreased when compared with healthy rats group (G1) and oral candidiasis immunosuppressed rats treated with hyperbaric oxygen 2,4 ATA 3x30 minutes/day for five days (G3). The decrease in serum albumin levels was likely because of enhanced leakage in the outside vascular system.[17] It also indicates a disruption in liver hepatocytes function, as hepatocytes are an important part of the liver that is responsible for metabolizing drugs.[4] Continuous use of immunosuppressant drugs could resulting in hepatocytes to work harder, which then caused injury and reduced its function.[5] A previous study using dexamethasone as immunosuppressive drugs showed an increase in serum ALT and AST levels. The elevation of ALT and AST levels could show the damage of the hepatocellular liver.[16] Hepatocytes are also being the major part in albumin synthesis, the integrity of these cells will effect on albumin production.[17] This was similar to a previous study that showed a decreased in the amount of albumin caused by a reduced in production by hepatocytes.[19]

The impact of hyperbaric oxygen therapy on serum albumin has never been explained in prior studies.[14] In this study, the increased serum albumin level in G3 group was likely due to the antioxidant function possessed by albumin. Albumin becomes primary circulating antioxidant in the body, main extracellular source of thiols and reduced sulfhydryl group, which then act as scavengers of reactive oxygen and nitrogen species.[15,19] Albumin also known can decrease malondialdehyde levels, increased catalase activity, and glutathione levels significantly, therefore diminished reactive free radicals lead to oxidative damage, protected the tissues from highly reactive hydroxyl radicals, and impaired lipid peroxidation.[17,19] Increased oxygen level derived from oxygen-based therapy will be accompanied by increased production of its product, reactive oxygen and nitrogen species, which has a role in the pathogenesis of the disease.[11,19] However, oxygen therapy given at pressure 2,4 ATA will produce reactive oxygen species as a signaling molecule, in relevant levels for inducing antioxidants activity which can then accelerate the healing process of injured tissues, also will give benefits to regeneration of hepatocyte cells.[12] Hyperbaric oxygen therapy not only able to increase tissue oxygen level, but also could elevate growth factors and reduce inflammatory cytokines.[14] Reactive oxygen species derived from cyclic periods of hyperbaric and normoxic oxygen will affect the release of multiple growth factors by transducing signaling pathways, including those that lead to angiogenesis.[20] Giving hyperbaric oxygen therapy will modulate Nitric Oxide (NO) to enhance expression of multiple growth factors such as Vascular Endothelial Growth Factor (VEGF) and Fibroblast Growth Factor (FGF) which able to trigger neovascularization and angiogenesis for healing injured tissue.[20, 21] Hyperbaric oxygen therapy was able to reduce the inflammatory cytokines IL-1, IL-6, and TNF-α.[22] This was in line with the function of albumin which was capable of binding to inflammatory mediators, thus inhibited inflammatory signaling pathway and prevent inflammation in injured tissue. The previous study showed that albumin becomes an effective modulator of the innate immune system that could provide benefits in administration of acute-on-chronic liver failure.[23]

Based on the result in this study, it can be concluded that serum albumin levels of oral candidiasis immunosuppressed rats treated with hyperbaric oxygen 2,4 ATA 3x30 minutes/ day with 5 minutes interval breathing in normal air, given for five days,

shows the significant enhancing levels compared to those group without therapy. Further study can be designed to evaluate the number of hepatocytes and other biochemistry parameters such as malondialdehyde, catalase enzim, and glutathione, to find out the hepatocellular liver function in oral candidiasis immunosuppressed rats model.

References

1. Vila T, Sultan AS, Montelongo-Jauregui D, Jabra-Rizk MA. Oral candidiasis: a disease of opportunity. J Fungi (Basel). 2020;6(1):15.
2. Zhang M, Yang X, Wang D, Yu C, Sun S. Antifungal activity of immunosuppressants used alone or in combination with fluconazole. J Appl Microbiol. 2019;126(5):1304–17.
3. Keerthi M, Reddy GS, Shekar PC, Chandra KL, Kumar KK, Reddy B. A study on isolation, identification, and antifungal susceptibility of various oral candidal species in renal transplant patients. J NTR Univ Health Sci [serial online]. 2015 [cited 2020 Jul 1];4:170-5. Available from: http://www.jdrntruhs.org/text.asp?2015/4/3/170/165399.
4. Jeanne Louise Schonborn. The role of the liver in drug metabolism. Anaesthesia Tutorial of the Week. [cited 2020 Jul 2] Available from: https://www.wfsahq.org/components/com_virtual_library/media/f7d652ac786de56a4a5832208294e382-ac7f3d7a04a43cfa854d58102cd229eb-179-The-role-of-the-liver-in-drug-metabolism.pdf
5. Prasetiawan E, Sabri E, Ilyas S. Gambaran histologis hepar mencit (Mus musculus L.) strain ddw setelah pemberian ekstrak n-heksan buah andaliman (Zanthoxylum acanthopodium Dc.) Selama masa pra implantasi dan pasca implantasi. Jurnal Online Saintia Biologi. 2012; 1(1):1-6.
6. Philip Hall and Johnny Cash. What is the real function of the liver 'function' tests?. Ulster Medical Journal. 2012;81(1):30–6.
7. George Kasarala, Hans L. Tillmann. Standard liver tests. Clinicla Liver Disease a Multimedia Review Journal. 2016;8(1):13–8.
8. Joana R. Carvalho, Mariana Verdelho-Machado. New insights about albumin and liver disease. Ann Hepatol. 2018;17(4):547–60.
9. Anna Skiada, Fanny lanternier, Andreas H. Groll, Livio Pagano, Stephen Zimmerli, Raoul Herbrecht, et al. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidlines from the 3rd European conference on infections in leukimia (ECIL 3). Haematologica. 2013:98(4):492–501.
10. Fanny Margaretha Laihad, I Ketut Sudiana, M Guritno. Hyperbaric Oxygen Therapy on mucormycosis infection in oral cavity. Folia Medica Indonesiana. 2017; 53(2):163–8.
11. Agni Febrina Pargaputri dan Dwi Andriani. Pengaruh pemberian terapi oksigen hiperbarik terhadap jumlah limfosit darah pada kandidiasis oral imunosupresi model. Denta Jurnal Kedokteran Gigi. 2018;12(2):36.
12. Yun Sun, Yankai Wen, Chanjuan Shen, Yuanrun Zhu, Wendong You, Yuanyuan Meng, et al. Hyperbaric oxygen therapy in liver disease. Int J Med Sci. 2018;15(8):782–7.
13. Andriani D, Pargaputri AF. Enhance of IL-22 expression in oral candidasis immunosuppressed model with Acanthus ilicifolius extract therapy. IOP Conference Series : Earth and Environmental Science 217. 2019:1–6.
14. Irawan H, Semadi IN, Devi A. Effect of hyperbaric oxygen therapy to improve serum albumin for patients with diabetic foot ulcers. Biomed Pharmacol J. 2018;11(1):569–75.
15. Bernardi M, Maggioli C, Zaccherini G. Human albumin in the management of complication in liver chirrosis. Critical Care. 2012;16(211):1–7.
16. Rosida A. Pemeriksaan laboratorium penyakit hati. Berkala Kedokteran. 2016;12(1):123–31.
17. Saad RA, FathelBab MF, El-Saba AA, Shalaby. AA. The effect of albumin administration on renal dysfunction after experimental surgical obstructive jaundice in male rats. Journal of Taibah University for Science. 2016;10(6):877–86.
18. MY Taslipinar, I Aydin, U Kaldirim, FN Aydin, M Agilli, YE Eyi, et al. Hyperbaric oxygen treatment and N-acetylcysteine ameliorate acetaminophen-induced liver injury in a rat model. Hum Exp Toxicol. 2013;32(10):1107–16.
19. Garcovich M, Zocco MA, Gasbarrini A. Clinical use of albumin in hepatology. Blood Transfus. 2009;7(4):268–77.
20. Prameswari N, Sunaryo IR, Damayanti DW, Pargaputri AF. The influence of hyperbaric oxygen therapy (HBOT) to intercausal relationship between blood vessels, osteoblast, and new bone formation during maxillary

suture expansion. Padjadjaran Journal of Dentistry. 2020; 32 (1):14–21.

21. Dirmadana RA, Mediani GS, Sandana IKI, Alief F, Yasin JJ, Brahmanta A. Inovasi Stichopus hermanii dan TOHB dalam meningkatkan jumlah fibroblas pada ligamen periodontal. Denta Jurnal Kedokteran Gigi. 2017;11(1):15–24.

22. Yasin JJ, Brahmanta A, Pargaputri AF. Inovasi terapi oksigen hiperbarik dan Stichopus hermanii terhadap jumlah makrofag pada ligamen periodontal antara daerah tekanan dan tarikan selama pergerakan gigi ortodonti. Denta Jurnal Kedokteran Gigi. 2018;12(1):1–10.

23. Arroyo V, Clària J. Acute-on-Chronic liver failure, human serum albumin, and immune modulation: the beginning of an exciting adventure. Clin Gastroenterol Hepatol. 2018;16(5):633-636.