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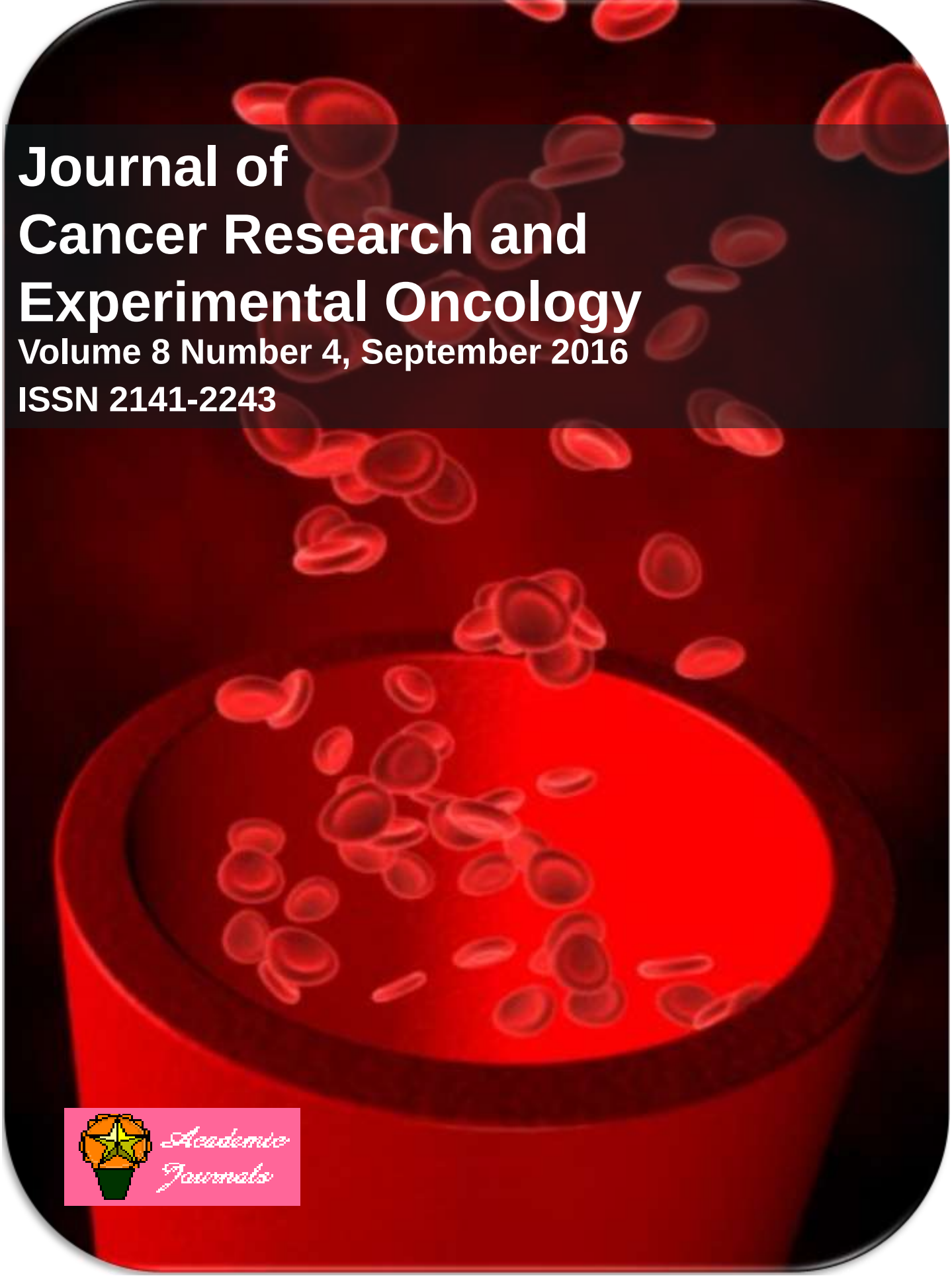

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The Acknowledgments of people, grants, funds, etc should be brief.

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Journal of Cancer Research and Experimental Oncology

Full length Research

Mean platelet volume and mean platelet volume/platelet count ratio as markers for hepatocellular carcinoma in patients with chronic hepatitis C virus related cirrhosis

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Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. The lack of efficient and precise HCC biomarkers prevents early detection resulting in a poor prognosis. Recently, mean platelet volume (MPV) and MPV/platelet count (PC) ratio have been proposed as potential markers of HCC. This study was carried out to verify MPV and MPV/PC ratio in diagnosis of HCC in Egyptian patients with chronic hepatitis C related liver cirrhosis. One hundred and fifty chronic hepatitis C (CHC) patients with chronic hepatitis, cirrhosis or HCC were enrolled in the study. The levels of alphe feto protein (AFP), MPV and MPV/PC ratio were determined compared to 50 healthy persons. MPV and MPV/CP ratio were higher in patients with cirrhosis and those with HCC. The cut off level for MPV for detection of HCC was 10.1 fl, with sensitivity of 70% and specificity of 57%. At a cut off level of 0.82, the sensitivity of MPV/CP ratio was 79.6% and specificity was 72.7%. AFP showed sensitivity 80% and specificity 82% at cut-off level of 16.9 ng/dl. MPV and MPV/PC ratio are less sensitive and specific than AFP as markers for HCC; they may be used only in association with other markers to improve sensitivity of tumor detection.

Key words: Hepatocellular carcinoma, mean platelet volume, platelet count, cirrhosis, hepatitis C.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver and remains a leading cause of death worldwide (Torre et al., 2012). The diagnosis of HCC can be difficult as patients usually have no symptoms other than those related to their chronic liver disease. The most commonly used marker for HCC is the serum alpha-fetoprotein (AFP) concentration. However, analysis of recent studies showed that AFP determination lacks adequate sensitivity and specificity for diagnosis (Lok et al., 2010). The lack of efficient and precise HCC biomarkers prevents early detection resulting in a poor prognosis.

Disorders of platelets count are common in various stages of liver diseases. Thrombocytopenia tends to

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predominate in patients with cirrhosis whereas normal, or even higher counts, including thrombocytosis are more common in patients with HCC (Carr et al., 2014; Carr and Guerra, 2013).

Mean platelet volume (MPV) is a parameter of routine blood count that provides an insight into platelet function and activation (Bath and Butterworth, 1996). Changes of MPV have been actively investigated in many liver diseases (Ceylan et al., 2014; Cho et al., 2013). MPV values were found to be elevated in patients with nonalcoholic fatty liver disease, intrahepatic cholestasis of pregnancy, chronic hepatitis, and liver cirrhosis (Cho et al., 2015; Kocabay et al., 2014; Karagoz and Tanoglu, 2014; Purnak et al., 2013; Celikbilek et al., 2013; Balta et al., 2013; Ozhan et al., 2010; Kebapcilar et al., 2010). MPV had been found to be correlated positively with the severity of histological grade in patients with primary biliary cirrhosis (PBC) (Tahtaci et al., 2015). Recently, MPV and MPV/platelet count (PC) ratio have been proposed as candidate markers for the diagnosis of HCC in patients with chronic liver disease (Cho et al., 2012; Kurt et al., 2011).

This study was carried out to verify the value of MPV and MPV/PC ratio in diagnosis of HCC in Egyptian patients with chronic hepatitis C (CHC) related liver cirrhosis.

MATERIALS AND METHODS

One hundred and fifty CHC patients plus fifty healthy volunteers were enrolled in the study. Patients were classified according to their clinical, laboratory and imaging characteristics into 3 equal groups: 50 patients with CHC without liver cirrhosis, 50 patients with liver cirrhosis due to CHC and 50 HCC patients on top of CHC liver cirrhosis. 50 healthy volunteers were also recruited as a control group. All control subjects were confirmed to have normal liver with no viral hepatitis, significant alcohol consumption or other chronic liver diseases.

The diagnosis of cirrhosis was based on clinical, laboratory, and imaging findings. The diagnosis of HCC was made by the presence of HCC radiological hallmarks in imaging technique (computed tomography (CT) and/or dynamic magnetic resonance imaging (MRI)) ± histopathological examination if needed (Bruix and Sherman, 2011; European Association, 2012).

Inclusion criteria included age above 18 years and positive PCR for hepatitis C virus (HCV) RNA. Patients with other causes of liver disease, sepsis, malignancy other than HCC, diabetes mellitus, dyslipidemia, rheumatologic diseases, advanced cardiac, renal or other chronic disease were excluded from this study.

The study was conducted with the approval of the Ethics Committees of National Liver Institute, Menoufiya University, Egypt. All contributors gave written informed consent prior to participation. The work has been carried out in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments in humans.

All patients were subjected to full history taking and complete physical examination, laboratory tests including complete blood count particularly platelets count (PC) and mean platelet volume (MPV), liver profiles, serum AFP level, hepatitis markers (HCV Ab, HBsAg, HBc total Ab) and HCV RNA PCR. Abdominal ultrasonography, triphasic abdominal CT and/or dynamic MRI were performed stressing on liver size, texture, focal lesion, portal vein diameter and patency, spleen size and presence of ascites.

Statistical analysis

Data were statistically analyzed using IBM® SPSS® Statistics® version 21 for Windows. Data were expressed as mean ± standard deviation for numerical data and number with percentage for ordinal and nominal variables.

Comparisons between two groups of HCC regarding lesions number and presence of portal vein thrombosis were performed using Mann-Whitney test. Comparisons between all studied groups were performed by one-way analysis of variance (ANOVA) test. If $p<0.05$, sub-analysis was done using Scheffé's method for post hoc test.

Chi-squared test (χ^2) and Fisher exact test were used for categorical data analysis. The receiver operating characteristic (ROC) curve analysis was used for detection of the cutoff value of AFP, MPV and MPV/PC ration.

All p-values are 2 tailed, with values <0.05 considered statistically significant.

RESULTS

Patients characteristics

The demographic and biochemical characteristics of the 3 groups of patients and controls are shown in Table 1. No significant differences regarding age or gender distribution existed between groups.

Platelets markers and AFP

The levels of AFP, MPV and MPV/PC ratio were determined in all patients and compared with 50 healthy persons. MPV levels and MPV/PC ratios showed significant difference among groups ($P<0.001$). Mean level of MPV was 8.9±1.8 in chronic hepatitis, 10.8±1.4 in patients with liver cirrhosis, 10.9±1.7 in HCC patients and 9.9±0.9 fl in controls (Figure 1). MPV/PC ratio was 0.49±0.14 in chronic hepatitis, 1.48±0.79 in patients with liver cirrhosis, 1.33±0.7 in HCC patients and 0.37±0.13 fl 10^{-4} μl^{-1} in controls (Figure 2).

By post hoc test, MPV and MPV/CP ratios were higher in patients with HCC and in patients with liver cirrhosis ($P<0.001$) when compared with controls and patients with CHC. However, no significant differences were found between patients with LC and those with HCC regarding platelets count ($P=0.98$), MPV ($P=0.94$) and MPV/PC ratio ($P=0.69$). Marked elevation of AFP level was observed in patients with HCC in comparison with healthy control subjects, patients with CHC and patients LC ($P<0.001$) (Figure 3).

AFP was significantly higher in patients with multiple focal lesions than in patients with single HCC ($p<0.01$). MPV and MPV/PC ratio had no association with local lesion number in HCC patients ($p =0.97$ and 0.76, respectively). No correlation was found between levels of studied markers and presence of portal vein thrombosis

Table 1. The demographic and biochemical characteristics of the studied groups.

Variable	Control	HCV without LC	HCV with LC	HCC	P	Significant Post Hoc
Age	54.9±6.2	54.6±6.4	52.3±5.9	55.0±6.1	0.08	-
Male gender	43 (86%)	45 (90%)	41 (82%)	45 (90%)	0.584	-
Bilirubin	0.7±0.2	0.8±0.2	2.6±2.1	2.0±1.9	0.001	P2, P3, P4, P5
Albumin	4.2±0.5	4.3±0.4	2.7±0.6	3.1±0.5	0.001	P2, P3, P4, P5
AST	16.5±5.5	49.0±30.0	80.2±42.0	91.3±70.2	0.001	P1, P2, P3, P4, P5
ALT	16.4±5.1	59.2±42.6	39.0±22.4	57.2±29.7	0.001	P1, P2, P3, P4, P5
Prothrombin	98.7±1.7	94.6±3.9	51.0±14.0	54.4±14.3	0.001	P2, P3, P4, P5
AFP	7.1±5.4	10.1±10.7	31.1±83.2	239.5±770.7	0.001	P3, P5, P6
Platelets ($\times 10^3 \mu L$)	299±90	193±61	99±73	105±58	0.001	P1, P2, P3, P4, P5
MPV (fl)	9.9±0.9	8.9±1.8	10.8±1.4	10.9±1.7	0.001	P1, P2, P3, P4, P5
MPV/PC (fl 10^{-4} μl^{-1})	0.37±0.13	0.49±0.14	1.48±0.79	1.33±0.7	0.001	P2, P3, P4, P5

P: One-way ANOVA between all groups, P1: Post Hoc test between controls and CHC group, P2: controls and LC, P3: controls and HCC, P4: CHC and LC, P5: CHC and HCC, P6: LC and HCC. HCV: Hepatitis C virus, LC: liver cirrhosis, HCC: hepatocellular carcinoma, MPV: mean platelets volume, PC: platelets count, ALT: alanine aminotransferase, AST: aspartate aminotransferase

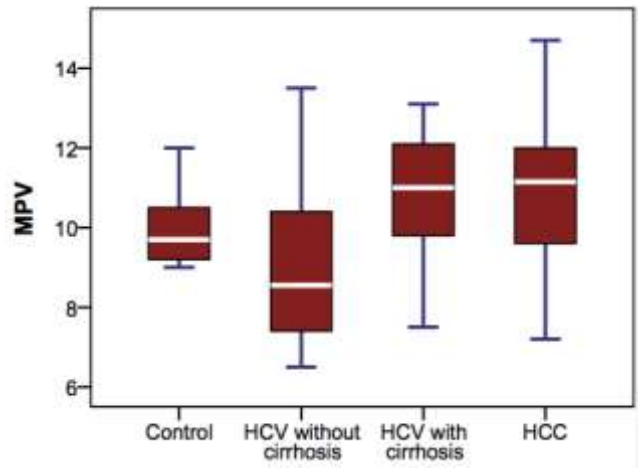

Figure 1. Mean level of MPV among the studied groups.

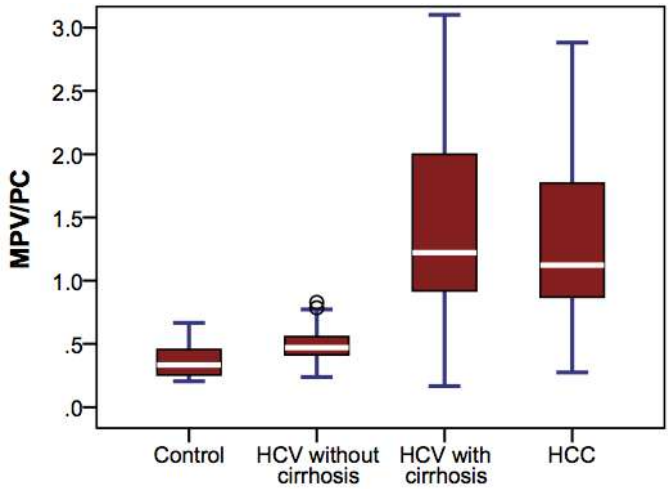

Figure 2. MPV/PC ratio among the studied groups.

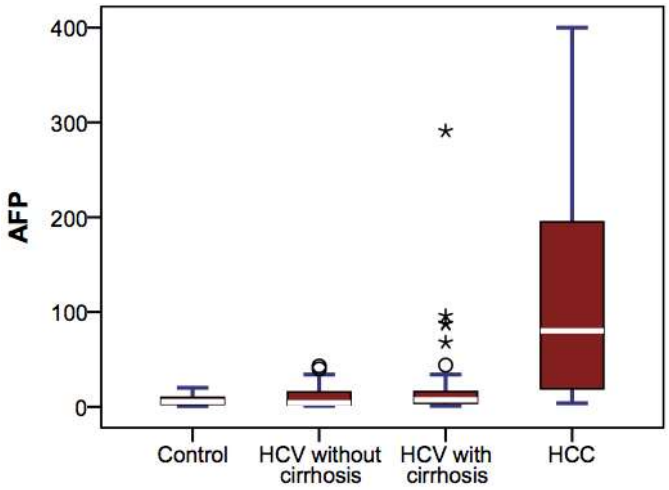

Figure 3. AFP level among the studied groups.

Table 2. Comparison of AFP, MPV and MPV/PC in relation to portal vein patency and focal lesions number in HCC patients.

Test	HCC patients		P*
	Patent PV (N=44)	PVT (N=6)	
AFP	119.77±153.98	1117.45±2136.82	0.08
MPV	10.90±1.74	11.07±1.85	0.82
MPV/PC	1.3±0.63	1.59±1.18	0.83
	Single focal lesion (N=28)	**Multiple focal lesions (N=22)**	
AFP	69.56±80.65	455.8±1135.8	0.003
MPV	10.94±1.53	10.88±2.0	0.97
MPV/PC	1.35±0.68	1.31±0.75	0.76

*Using Mann-Whitney U test, MPV: Mean platelets volume, PC: platelets count, PV: portal vein, PVT: portal vein thrombosis.

Table 3. Receiver operating characteristic (ROC) for AFP, MPV and MPV/PC.

Test	Area under the curve	Std. Error	*P*	95% Confidence interval	
				Lower bound	Upper bound
AFP	0.884	0.027	< 0.001	0.832	0.936
MPV	0.670	0.046	< 0.001	0.579	0.760
MPV/PC	0.777	0.034	< 0.001	0.710	0.844

(Table 2).

Using receiver operating characteristic (ROC) curve analysis, the cut off level for MPV for detection of HCC was 10.1 femtolitre (fl), with sensitivity 70%, specificity 57.3%, area under the curve (AUC): 0.67 (0.579 to 0.760), p <0.001. At a cut off level of 0.82 fl 10^{-4} μl^{-1}, the sensitivity of MPV/PC ratio was 79.6%, specificity was 72.7%, AUC was 0.777 (0.710 – 0.844), p <0.001 (Table 3).

Both MPV level and MPV/PC ratio showed lower sensitivity and specificity for diagnosis of HCC than AFP which showed sensitivity 80.1% and specificity 82% at cut-off level of 16.9 ng/dl, AUC: 0.884 (0.832 to 0.936), p <0.001 (Table 4 and Figure 4).

When the cut off levels for both AFP and MPV were used together, had a specificity of 92%, while when used separately, they had a sensitivity of 92%, but specificity dropped to 47.3%. Similarly, concurrent use of AFP and

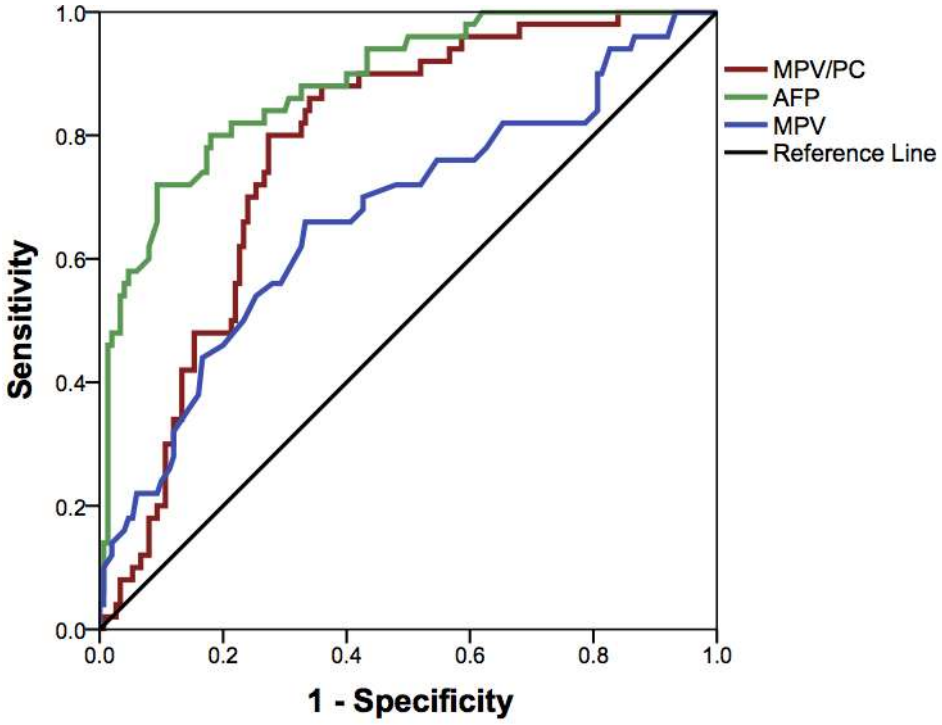

Figure 4. Sensitivity, specificity, PPV, NPV and accuracy of AFP, MPV and MPV/CP in the diagnosis of HCC.

Table 4. Sensitivity, specificity, PPV, NPV and accuracy of AFP, MPV and MPV/CP in the diagnosis of HCC.

Variable cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
AFP	80.1	82	59.09	91.79	81
MPV	70	57.33	35.35	85.15	60.5
MPV/CP	79.6	72.7	48.78	91.53	74
AFP or MPV	92	47.33	36.8	94.67	58.5
AFP and MPV	56	92	70	86.25	83
AFP or MPV/PC	98	60.67	45.37	98.91	70
AFP and MPV/PC	60	93.33	75	87.5	85

MPV: Mean platelets volume, PC: platelets count, PPV: positive predictive value, NPV: negative predictive value.

MPV/PC ratio cut off levels showed sensitivity of 60% and specificity of 93.3%, whereas discrete use of either of them revealed higher sensitivity (98%) and lower specificity of 60.7% (Table 4).

DISCUSSION

Determination of mean platelet volume (MPV) is a routine measure that is part of a complete blood count. MPV has been investigated in various clinical fields including chronic liver diseases.

In the literature, there are only a few studies examining the relationship between MPV or MPV/PC and HCC (Cho et al., 2013; Kurt et al., 2011). Hence, this cross-sectional study conducted involves 150 patients with various clinical spectrums of HCV infection including patients without cirrhosis, with liver cirrhosis and those with HCC on top of HCV related liver cirrhosis, aiming to explore the validity of MPV and MPV/PC as diagnostic tool for HCC.

Increased interleukin-6 (IL-6) production is implicated in the pathogenesis of hepatocellular carcinoma (HCC) (Wong et al., 2009). IL-6 is strong inflammatory indicator that seems to be useful in predicting the development of HCC and treatment outcome in patients receiving loco-regional therapy (Wong et al., 2009; Jang et al., 2012). High serum levels of IL-6 are associated with

independent increase in HCC risk (Ohishi et al., 2014).

On the other hand, high IL-6 levels enhance platelet generation in the bone marrow. Thus, MPV values increase because of the increase in the number of young platelets entering into circulation and rapid activation and growth of platelets (Kaser et al., 2001). For these reasons, we would expect to find increased MPV in patients with HCC.

Chronic hepatitis caused by hepatitis C virus (HCV) has been documented as a possible cause of thrombocytopenia, even in the absence of cirrhosis (Fouad, 2013; Osada et al., 2012). This was demonstrated in the present study as the mean platelet counts were significantly lower in patients with CHC than control subjects. Additionally, mean platelet count in patients with liver cirrhosis was significantly lower than non-cirrhotic patients and the control subjects. This is the expected abnormality of platelet count in cirrhosis. The mechanisms responsible for thrombocytopenia in chronic liver disease include suppression of platelet production in the bone marrow (Wang et al., 2004), decreased activity of the hematopoietic growth factor, thrombopoietin (Rios et al., 2005) and splenic sequestration of platelets in portal hypertension (Rios, 1966; Peck-Radosavljevic, 2000; Afdhal et al., 2008), which is produced primarily in the liver. There is also increased destruction of platelets in patients with chronic liver disease by immunological mechanisms that result from increased levels of platelet-associated immunoglobulins (PAIgG) (Pereira et al., 1995; Sanjo et al., 2003).

Mean platelet count in patients with HCC was higher than that in cirrhosis in our study, but did not reach significant level. High platelet count and even thrombocytosis is common in many malignant diseases (Carr, 2014) including those of the ovary (Stone et al., 2012), gastrointestinal tract (Voutsadakis, 2014), and liver (Carr and Guerra, 2013; Hwang et al., 2004).

Increased platelet count in patients with malignancies may be explained by the link between platelets and angiogenesis (Pinedo et al., 1998; Olas et al., 1999; Banks et al., 1998). Certain types of malignancy can activate platelets *in vitro* through direct contact, release of ADP, production of thromboxane A2 or cancer procoagulant, generation of thrombin, or activation of the tumor-associated proteinases (Olas et al., 1999). In the presence of vascular endothelial growth factor (VEGF), which is a platelet-derived cytokine, endothelial cells promote platelet aggregation (Verheul et al., 2000). Adhesion and aggregation of activated platelets are accompanied by the release of many potential angiogenesis regulators such as VEGF-A (Ukropec et al., 2000), VEGF-C (Wartiovaara et al., 1998) and platelet-derived endothelial cell growth factor (PD-ECGF) (Griffiths and Stratford, 1997). These observations suggest that platelets may play an active and causative role in tumor angiogenesis (Pinedo et al., 1998).

Carr et al. (2014) reported that extracts from normal human platelets could stimulate growth *in vitro* in several human HCC cell lines. The extracts also inhibited apoptosis and stimulated HCC cell migration and invasion. Platelets therefore can be considered a micro-environmental factor in HCC cell growth (Carr et al., 2014).

Our study showed that the patients with HCC have higher AFP rather than cirrhotic patients; however, MPV and MPV/PC ratio values failed to show significant difference between patients with LC and HCC. Both values had higher levels in patients with liver cirrhosis than CHC non-cirrhotic patients. These findings suggest that MPV and MPV/PC may be potential markers for liver fibrosis in CHC patients. Similarly, Purnak et al. (2013) reported that MPV is increased in CHC patients with advanced fibrosis. In patients with cirrhosis, splenomegaly-induced platelet sequestration has been considered to be the main reason for the decrease in platelet survival, and hence, increase in MPV (Aster, 1966).

The cut-off value for MPV in our study for the detection of HCC in cirrhotic patients was 10.1 fl using ROC analysis (sensitivity: 70%, specificity: 57.3%). On the other hand, Kurt et al. (2011) calculated the cut-off value for MPV for the detection of HCC as ≥ 9.2 fl with sensitivity of 68.3% and specificity of 69.2% (Kurt et al., 2011). Additionally, they reported that serum MPV levels showed higher sensitivity for diagnosis of HCC than AFP (Kurt et al., 2011). On the contrary, we showed that serum MPV level was less sensitive (70%) for diagnosis of HCC than AFP (78%). Kurt et al. (2011) reported lower specificity of serum MPV levels (69.2%) for diagnosis of HCC than that of AFP (89.5%) and this agrees with our result that shows also lower specificity of serum MPV levels (57.33%) than AFP (82%).

In our study when the cut off levels for both AFP and MPV were put together; the specificity increased to 92%, while when used separately, they had also a higher sensitivity of 92%. On the other hand, using both AFP and MPV/PC ration had a high specificity (93.3%), while when used independently, sensitivity improved to 98%. Comparable results were reported by Kurt et al. (2011).

There are a few limitations in the current study. The cross-sectional nature of this study provides only a snapshot; it may provide different results if another time frame had been chosen and prevalence-incidence bias is expected in this study. Thrombopoietin levels were not done in the present study, as well as other inflammation markers such as neutrophil–lymphocyte ratio and serum C-reactive protein level.

MPV values may be affected by smoking habits, hypertension, diabetes, dyslipidemia, atherosclerotic diseases, venous thromboembolism, rheumatologic diseases, and inflammatory bowel diseases (Gasparyan et al., 2011). Although, patients with most of the aforementioned factors were not included in our study. The possibility that the presence of subclinical aspects

that may affect our results cannot be ignored.

Conclusion

MPV is quick, easy and cheap to measure. However, MPV and MPV/PC ratio are less sensitive and specific than AFP as markers for HCC. Therefore, they may be used only in association with other markers like AFP to improve sensitivity of tumor detection.

Further studies with larger samples should evaluate them as non-invasive markers for fibrosis and as adjunctive indicator for HCC in patients with chronic liver disease. Further follow-up of the patients with CLD and higher MPV values (**>**10.1) to observe the development of HCC would provide more reliable data.

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Conflict of interests

The authors have not declared any conflict of interests.

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Prevalence of unilateral arm lymphedema among breast cancer patients one year after completing treatment at Cancer Diseases Hospital in Lusaka

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Lymphedema of the arm and/or hand is a long-term complication of breast cancer treatment. Accurate estimates of the incidence and prevalence of lymphedema are lacking, as are the effects of this condition on overall quality of life. The objective of this study was to determine the prevalence of unilateral arm lymphedema among breast cancer patients one year after completion of treatment at Cancer Diseases Hospital. The prevalence of unilateral arm lymphedema controlling for cancer stages and treatment types were determined using a cross sectional study. Arm circumference of all breast cancer clients was measured to determine the prevalence of lymphedema. Prevalence of arm lymphedema (95% CI) was mild 60%, moderate was 28% and severe lymphedema was at 12%, respectively with stage I breast cancer patients, only presented with mild form of lymphedema. The study showed that lymphedema after breast cancer is common but mostly mild; increasing the awareness of health professional regarding early diagnosis can help minimize the morbidity of this disease post-surgery and radiation treatments among breast cancer patients.

Key words: Lymphedema, breast cancer, patients, arm lymphedema.

INTRODUCTION

Due to advances in detection and treatment, increasing numbers of women are diagnosed with and surviving breast cancer each year in Zambia (CDH, 2012). Breast cancer is the second most common cancer affecting women and accounts for 9% of all histologically proven cancers and accounts for 8% mortality rate among patients admitted at Cancer Diseases Hospital in Lusaka (CDH 2012).

Lymphedema or "big arm" is an increase in volume of the upper limb due to accumulation of water, protein and fats following damage to the lymphatic system caused by axillary lymph node clearance (Clark, 2005). Lymphedema can occur after any cancer or its treatment that affects lymph node drainage (NCI, 2015). Affected patients can experience swelling, pain, arm tightness, heaviness of the arm, and recurrent skin infections

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(Pyszel, 2006; Fu and Rosedale, 2009). Breast cancer-related lymphedema due to impaired lymphatic drainage from the arm secondary to axillary surgery and/or radiotherapy is one of the common side effects occurring in 12 to 54% of cases (Clark, 2005; Fu and Rosedale, 2009; Hayes et al., 2012).

As an incurable and progressive condition characterized by chronic swelling of the limb, it can cause significant physical, functional, psychological, and social morbidity and may severely impact health related quality of life (HRQoL), thus downgrading HRQoL (Keeley et al., 2010). Breast cancer patients may find lymphedema more distressing than mastectomy, because hiding the physiological manifestations and loss of function of lymphedema is harder. Overall, these factors lead to decreased HRQoL for breast cancer patients (Petrek, 1998). Breast cancer patients do not die of lymphedema, but their HRQoL is severely impaired (Maree, 2011). Therefore, the purpose of the study was to determine the prevalence of unilateral arm lymphedema one year after completing breast cancer treatment.

METHODS

The study was conducted at the Cancer Diseases Hospital (CDH) a modern specialized tertiary hospital offering radiation therapy, chemotherapy and hormonal cancer treatments. The hospital serves as a national referral centre for all cancers nationwide; the catchment population comprises all 107 districts and 10 provinces of Zambia. A cross-sectional study design was used and 125 breast cancer patients who were willing to participate in the study were conveniently selected. The study population consisted of all breast cancer patients who had been visiting CDH breast review clinics from April 2006 to December 2013, were 18 years of age and above, had mastectomy and axillary dissection, completed radiation therapy, chemotherapy, hormonal therapy, had unilateral breast cancer with stages I, II, and III disease.

Breast cancer patients who had lymphedema in both upper limbs, had evidence of recurrent breast cancer in axilla and stage 4 diseases were excluded. Based on 9% prevalence of breast cancer cases at CDH, 125 participants were enrolled in the study in order to identify true prevalence with precision of +/-5% and 95% confidence interval. Before the commencement of the study, the University of Zambia, Biomedical and Research Ethics Committee approved the research study (Ref. No. 2014-Apr-003). The purpose, risks and benefits of the study were explained to the participants to enable them make informed consent to participate in the study. Those who agreed to participate in the study signed a consent form before being interviewed using a modified interview schedule. Anonymity and confidentiality were maintained by using serial numbers on the interview schedule. The interview schedules were locked away and only the research team had access to raw data.

The data collection tool had 2 sections, (a) demographic data and (b) arm circumference measurements, disease stage and type of treated received. Arm circumferences of all breast cancer patients were measured to determine the prevalence among those with lymphedema. Circumferential measurement points were at 10 cm above elbow crease, 7 cm below elbow crease, wrist, and mid-palm level using a non-stretch measuring tape. The contra lateral arm circumference at corresponding levels was used as a reference to determine lymphedema. Lymphedema was defined as an increase in arm circumference at any level by 2 cm or more compared to the contra lateral side. The severity of lymphedema was divided into 3 degrees (a difference in circumference up to 2 cm indicated mild lymphedema, a difference of 2, 1 to 5 cm was moderate lymphedema, and a difference of more than 5, 1 cm was considered severe lymphedema. Age, sex, educational status, marital status and employment status were obtained from the participant as well as the participants' files. The demographic data was required because it has been shown to influence lymphedema outcomes post breast cancer treatment.

Data was analyzed using STATA version 10. The prevalence of arm lymphedema was estimated using Stata 10.0 command proportion with options specifying the sub-groups. A bivariate analysis with Pearson's chi-squared test for association with p-value<0.05 between the hypothesized outcomes of interest among breast cancer patients with arm lymphedema was explored. Statistical significance was calculated using the chi square test.

RESULTS

Out of the 125 clients who participated in the study, 75 clients had mild lymphedema, 35 clients had moderate lymphedema and 15 had severe lymphedema (Table 1). Thirteen clients had stage I disease, 54 had stage II disease, while 58 had stage III disease (Table 2). All participants received surgery, radiation therapy, chemotherapy and hormonal therapy (Table 3). All the participants with stage I disease presented with a mild form of lymphedema (Figure 1).

The study sample consisted of 125 breast cancer patients aged 18 years and above. The respondents who were not married, divorced, separated and windowed were categorized as single while those married were categorized as married. Respondents who had no education and those with primary were categorized as having low education.

Respondents with secondary education were categorized as having moderate education; those with college and university education were categorized as having high education. The socio demographic data which was relevant in this study included age, gender, marital status, and highest education attained.

Data showed that lymphedema was common among those who were above 50 years (48.8%), followed by those between 34 and 49 years (29.6%) and less common between those aged between 18 to 33 years (21.6%). There were more female participants (98.4%) than males (1.6%). Most of the participants were married (64%) and their highest level of education attained was college/university (57%). Most of them were also employed (75%).

In this study, arm lymphedema was classified into mild, moderate and severe. Out of the 125 patients who participated in the study, 75 (60%) had mild lymphedema, 35 (28%) had moderate lymphedema and 15 (12%) had severe lymphedema (Table 2).

Three cancer stages were considered in this study. Table 3 indicates that 13 participants (10.4%) had stage I breast cancer, 54 (43.2%) had stage II breast cancer and 58 (46.4) had stage III disease. Therefore, stage III

Table 1. Demographic characteristics of the participants (n=125).

Variable	Frequency	Percentage
Age		
18 to 33	27	21.6
34 to 49	37	29.6
50 and above	61	48.8
Total	125	100
Gender		
Female	123	98.4
Male	2	1.6
Total	125	100
Marital status		
Single	45	36.0
Married	80	64.0
Total	125	100
Education status		
None/Primary	22	17.6
Secondary	31	24.8
College/University	72	57.6
Total	125	100
Occupation		
Employed	75	60.0
Unemployed	50	40.0
Total	125	100

Table 2. Categories of arm lymphedema among the respondents (n=125).

Category	Frequency	Percentage
Mild	75	60.0
Moderate	35	28.0
Severe	15	12.0
Total	125	100

Table 3. Lymphedema across cancer stages (n=125).

Stage of cancer	Frequency	Percentage
Stage I	13	10.4
Stage II	54	43.2
Stage III	58	46.4
Total	125	100

breast cancer was the commonest among the participants (Table 3).

Figure 1 shows the prevalence of arm lymphedema stages across the three stages of breast cancer in percentages (stages I, II, III). All patients with stage I disease had a mild form of arm lymphedema (100%).

Table 4. Breast cancer treatment received (n=125).

Treatment type	State	Frequency	%
Surgery	No	0	0
	Yes	125	100
Radiation therapy	No	0	0
	Yes	125	100
Chemotherapy	No	0	0
	Yes	125	100
Hormones	No	0	0
	Yes	125	100
Total	Yes	125	100

Table 5. Bivariate analysis with observed association between covariates, Pearson's chi-squared *p* values <0.05 between the hypothesized outcomes of interest among Breast Cancer Patients with Arm Lymphedema at Cancer Diseases Hospital in Lusaka, Zambia (n=125).

Covariates	Lymphedema
Patient's sex	1.36
	0.508
Patient's age	23.61
	<0.001*
Patient's marital status	22.47
	<0.001*
Patient's education	29.89
	<0.001*

Most of the participants had stage III breast cancer (mild 51.72, moderate 34.49 and severe stage of lymphedema 13.79).

All the 125 participants who were recruited in the study received surgery, chemotherapy, radiation therapy and hormonal treatment.

From the chi-squared association analysis, participant's age (p-value<0.001), marital status (p-value<0.001) and patients education (p-value<0.001) were determined to be those that were associated either with the outcome or independent variable of interest.

DISCUSSION

The International Society of Lymphology (ISL) classifies lymphedema into three stages, namely mild, moderate and severe (National Cancer Institute, 2015). It is important to diagnose and treat lymphedema when it is mild because those with mild lymphedema make up the cohort that gives rise to preventable severe, debilitating lymphedema (NCI, 2015). Women with mild lymphedema are more than three times more likely to develop severe lymphedema than women with no lymphedema (Norman et al., 2009).

A large percentage of the respondents who participated in this study were above 50 years of age (Table 1). The age range was from 18 to above 50 years. Lymphedema was common among those who were above 50 years (48.8%), followed by those between 34 and 49 years (29.6%) and less common between those aged between 18 and 33 years (21.6%). There were more female participants (98.4%) than males (1.6%). Most of the participants were married (64%) and their highest level of education attained was college/university (57%). Most of them were also employed (75%).

The present study showed a positive association with lymphedema and age ($p < 0.001$), gender ($p < 0.001$) education and marital status ($p < 0.001$) of the respondents (Table 5). Similarly, Pasket et al. (2013) reported a significant statistical association between marital status and lymphedema. Haghighat et al. (2013) in their study showed that lymphedema was significantly more prevalent in breast cancer patients with lower levels of education.

In the present study, lymphedema was also classified as mild, moderate and severe. As shown in Table 1, out of the 125 patients who participated in the study, 75 (60%) had mild lymphedema, 35 (28%) had moderate lymphedema and 15 (12%) had severe lymphedema (Table 2). Mild lymphedema was more common among breast cancer patients one year after completing breast cancer treatment in this study and the percentage of the

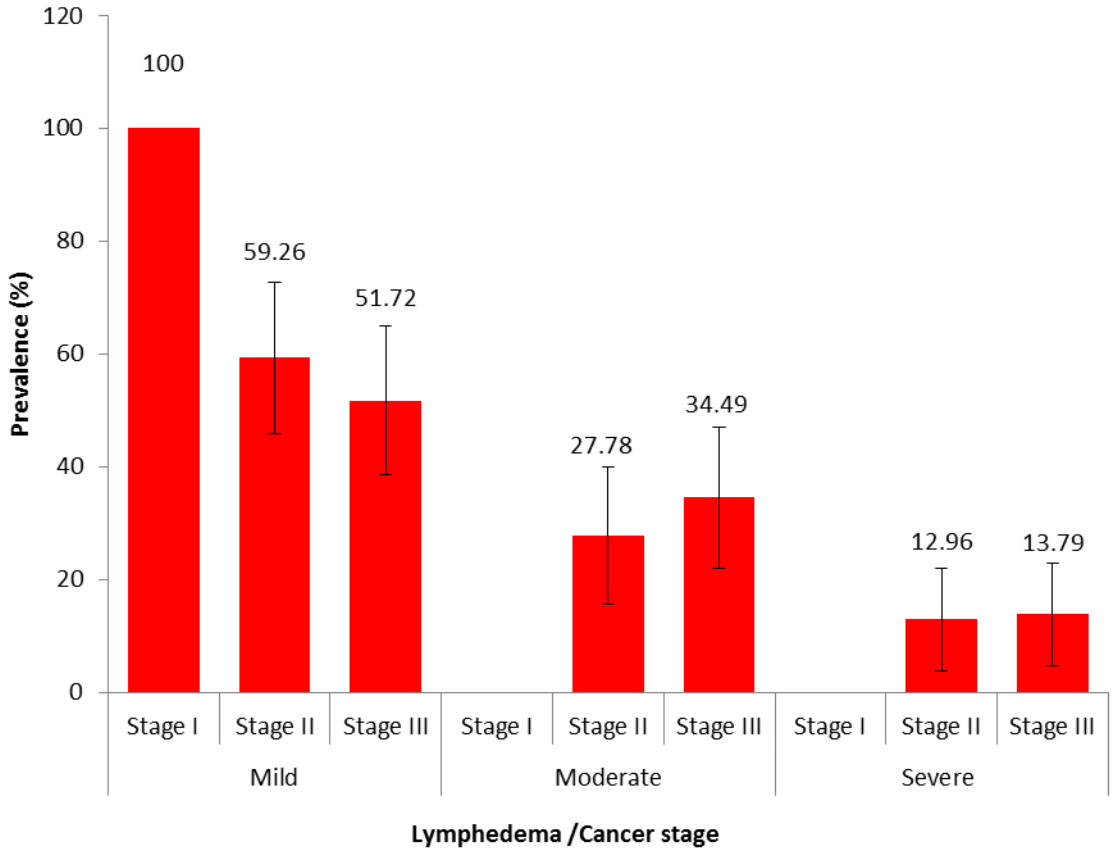

Figure 1. Lymphedema according to breast cancer stages (n=125).

respondents' lymphadema was high compared to other studies (Bar et al., 2012; Petrek, 1998).

With regards to the relationship between lymphedema and breast cancer stages among the study participants, the analysis showed that 13 (10.4%) patients with lymphedema had stage I disease, 54 (43.2%) had stage II disease, while 58 (46.4%) had stage III disease (Table 3). Therefore, more patients with stage III breast cancer had lymphedema. In our study, all stage I breast cancer patients had mild lymphedema which could be associated with infections. However, the incidence of lymphedema was statistically significantly higher in patients with advanced breast cancer (Stage III) than patients with early-stage breast cancer (Figure 1).

All the 125 participants who were recruited in the study received surgery, chemotherapy, radiation therapy and hormonal treatment (Table 4). Treatment modalities have been reported to as predictor factors of lymphedema by different studies. Moreover, the type of surgery (Ugur et al., 2013; Ozcinar et al., 2012; Park et al., 2008; Edwards, 2000; Schunemann and Willich, 1997), chemotherapy (Paskett et al., 2007; Deo et al., 2004), and radiotherapy (Lawenda et al., 2009; Park et al., 2008; Herd-Smith et al., 2001; Deo et al., 2004) have been shown to have a significant relation with the incidence of edema. Other studies have not found such association (Park et al., 2008; Petrek et al., 2001). In a study by Disipio et al. (2013), it was found that extensive surgery (chest wall and axilla) increased the risk of lymphedema and adjuvant therapy (radiation and chemotherapy) (Disipio et al., 2013). In the current research, none of these treatment modalities showed significant relation with lymphedema.

CONCLUSION

The study showed that lymphedema was common among breast cancer patients, but it was mostly mild. Therefore, providing lymphedema prevention education, early diagnosis, and treatment of lymphedema to those women who undergo more extensive axillary node dissection and/or radiation may reduce the risk of prevalent swelling or the severity if swelling does develop. In so doing, cancer survivors of all ages will ultimately enjoy better quality of life.

Conflict of Interests

The authors have not declared any conflict of interests.

Abbreviations:

CDH, Cancer Disease Hospital; **HRQoL,** health related quality of life; **NCI,** National Cancer Institution; **MEPI,** Medical Education Partnership Initiative; **SACORE,** Southern Africa Consortium for Research Excellence Zambia; **UNZA-SoM,** University of Zambia School of Medicine; **DNS,** Department of Nursing Sciences; **MSc,** Master of Science; **MOH,** Ministry of Health.

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