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Original Article

Etiologies and outcome of osteonecrosis of the femoral head: Etiology and outcome study in a Taiwan population

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Abstract

Background: Osteonecrosis of the femoral head (ONFH) is an important indication for total hip arthroplasty in Taiwan. We demonstrated the etiologies of ONFH and outcomes based on stratification of patients according to different etiologies.
Methods: We reviewed medical records and images from January 2000 to May 2010 in our database with the diagnosis of "osteonecrosis of the femoral head." We categorized all patients into different etiologies, including corticosteroid, alcohol, and idiopathic. All patients received subsequent follow up for ipsilateral precollapse ONFH and contralateral disease-free femoral head status after initial diagnosis.
Results: Of the 1153 patients who had undergone 1674 hip surgeries including core decompression and total hip replacement, alcohol use was the most prevalent etiology in our population (45.2%). Patients with corticosteroid- and alcohol-associated ONFH were younger and more likely to have bilateral disease. Patients with alcohol- or steroid-associated ONFH were found to have a higher rate of contralateral disease and faster progression of precollapse ONFH than patients who had or had not undergone core decompression.
Conclusion: Alcohol use had the greatest impact on ONFH in our population. Nonidiopathic ONFH patients had the worst outcome. Understanding the nature of progression of ONFH and incidence of contralateral disease may provide great prognostic value to detect and perform early intervention.

Keywords: avascular necrosis; etiology; femoral head; osteonecrosis; outcome

1. Introduction

More than 4000 primary total hip replacement (THR) surgeries are performed annually in Taiwan. Indications for primary THR in Taiwan have been reported to be greatly different from those in Norway and Sweden. Instead of osteoarthritic (OA) hip, osteonecrosis of the femoral head (ONFH) is the leading indication for primary THR, accounting for 46.9% of all indications.[1–3] For a patient with precollapse ONFH, conservative treatment or surgical intervention would be expected to prolong the duration to progress to the postcollapse status. Hip arthroplasty remains the main choice of treatment in patients with postcollapse ONFH. These patients are generally young, with great functional requirement, and a long life expectancy. Revision arthroplasty could be expected in their lifetime because of wear, loosening, or breakage of the implants, which would greatly impair the life quality of the patient and increase the burden on the medical service system.

There are several risk factors associated with the collapse of the femoral head, including the initial stage, lesion size, location, and sickle cell anemia.[4–9] Goker and Block[10] stated

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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that positive initial radiographic evidence at the contralateral hip indicated risk of progression to symptomatic disease or a more advanced stage. However, there had not been a study that compared the outcome of patients with ONFH among etiologies.

The aim of this study was to show the demographic data in our population and prognosis for ONFH patients with different etiologies. First, we demonstrated the prevalence of etiologies in our population. We also demonstrated the age at which patients had undergone surgeries and the proportion of bilateral disease. Second, we demonstrated the incidence of contralateral ONFH when unilateral ONFH was detected. Third, among the study groups, we showed the survival rate of patients with precollapse ONFH and their progress to postcollapse ONFH.

2. Methods

Medical records and all images including plain film, nuclear scan, or magnetic resonance image from a single medical center database, from January 2000 to May 2010, with the diagnosis of "osteonecrosis of femoral head" were reviewed by a single experienced orthopedist. Informed consent was obtained from each participant for this retrospective study. A total of 1500 patients fulfilled the search criteria that they had been treated as outpatients or inpatients. Patients with diagnosis of OA hip, rheumatoid arthritis of the hip, ankylosing spondyloarthropathy of the hip, developmental dysplasia of the hip, pigmented villonodular synovitis, Legg−Calvé−Perthes disease or femoral neck fracture but wrongly recorded as ONFH, missing images and medical records, or trauma-associated ONFH were excluded. We excluded 93, 110, and 144 patients because of wrong diagnosis, missing data, and trauma-associated ONFH, respectively. A total of 1153 patients who had undergone 1674 surgeries, including 354 core decompression surgeries and 1320 hip arthroplasty surgeries, were included. Patients who experienced hip fractures with subsequent ONFH were defined as trauma-associated ONFH. For precollapse ONFH cases, we performed core decompression without bone grafting or with nonvascularized trochanteric bone grafting. For postcollapse ONFH cases, hemiarthroplasty or total hip arthroplasty was performed. After the surgery, we arranged monthly follow ups during the first 3 months, then once every 3 months up to 1 year, and annually thereafter. During the follow up, plain films or magnetic resonance imaging (MRI) was taken to check for new onset or progression of the disease. If unilateral ONFH was found on the image before surgery, all subsequent images were checked for contralateral ONFH. The interval between the onsets of bilateral ONFH was recorded. For patients with precollapse ONFH, duration to progress to postcollapse ONFH was recorded.

All patients were categorized into the following three groups: alcohol users, corticosteroid users, and idiopathic. We defined alcohol users using the records of daily consumption of different types of alcoholic drinks including beer, wine, and liquors. Average daily amount was estimated as g of ethanol/d by multiplying average daily consumption of liquors in milliliters by the percentage of ethanol contained in the liquors. We defined corticosteroid users using the records of regular follow up at the outpatient department with a diagnosis indicated for regular corticosteroid use. To define idiopathic ONFH, we first excluded alcohol- or corticosteroid-associated ONFH. We reviewed medical records to rule out additional risk factors including Caisson disease, Gaucher disease, sickle cell anemia, vasculitis, polycythemia, coagulopathies, and disseminated intravascular coagulation. Patients were then recorded as idiopathic ONFH. In all three groups, sex, weight, height, body mass index (BMI), and age of patients who had undergone core decompression or arthroplasty were recorded.

Comparisons of patient characteristics were performed using chi-square test and analysis of variance with Tukey honest significant difference test for categorical and continuous variables, respectively. Univariate survival outcomes for patients with precollapse ONFH and contralateral disease-free femoral head status were estimated using the Kaplan−Meier method and compared using log-rank statistics. To determine whether observed differences in survival were independently associated with different etiologies, multivariate analysis was performed using the Cox proportional hazards model. In addition to etiologies, additional study variables included in the model were age, sex, body height, body weight, and whether the patient had undergone core decompression surgery. We used SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) for all statistical calculations.

3. Results

Patients underwent core decompression and hip arthroplasty surgeries at the average ages of 44.5 years and 50.2 years, respectively. Among these patients, the alcohol consumption group accounted for the most cases of ONFH (45.2%) in our population. The steroid (21.7%) and idiopathic (33.1%) groups accounted for the rest. Overall, 663 (59.1%) patients had bilateral ONFH. The proportion of bilateral ONFH was higher in the corticosteroid group (72.4%) than in the alcohol (62.5%) and idiopathic groups (45.3%). Patients who had undergone surgery for an unknown indication at an outside hospital in one hip and presented with ONFH in the contralateral hip were recorded "not determined" (Fig. 1). Among the 93 patients with other diagnosis but wrongly recorded as ONFH, the most common diagnosis was OA hip (59.0%). The most common indication for corticosteroid use was systemic lupus erythematosus (SLE; 43.6%; Table 1). Among the patients categorized as alcohol-associated ONFH, the average daily alcohol consumption was 86.21 ± 109.8 g (range 15−556 g).

Concerning the demographic data of these patients (Table 2), we found male preponderance (69.3%). Among the male patients, alcohol (62.1%) was the most important risk factor for ONFH. By contrast, idiopathic (49.2%) and corticosteroid-associated ONFH (43.7%) were more prevalent in female patients. Body height and weight were higher in the alcohol group than in others, however, BMI was not different. The average ages for patients undergoing core decompression and

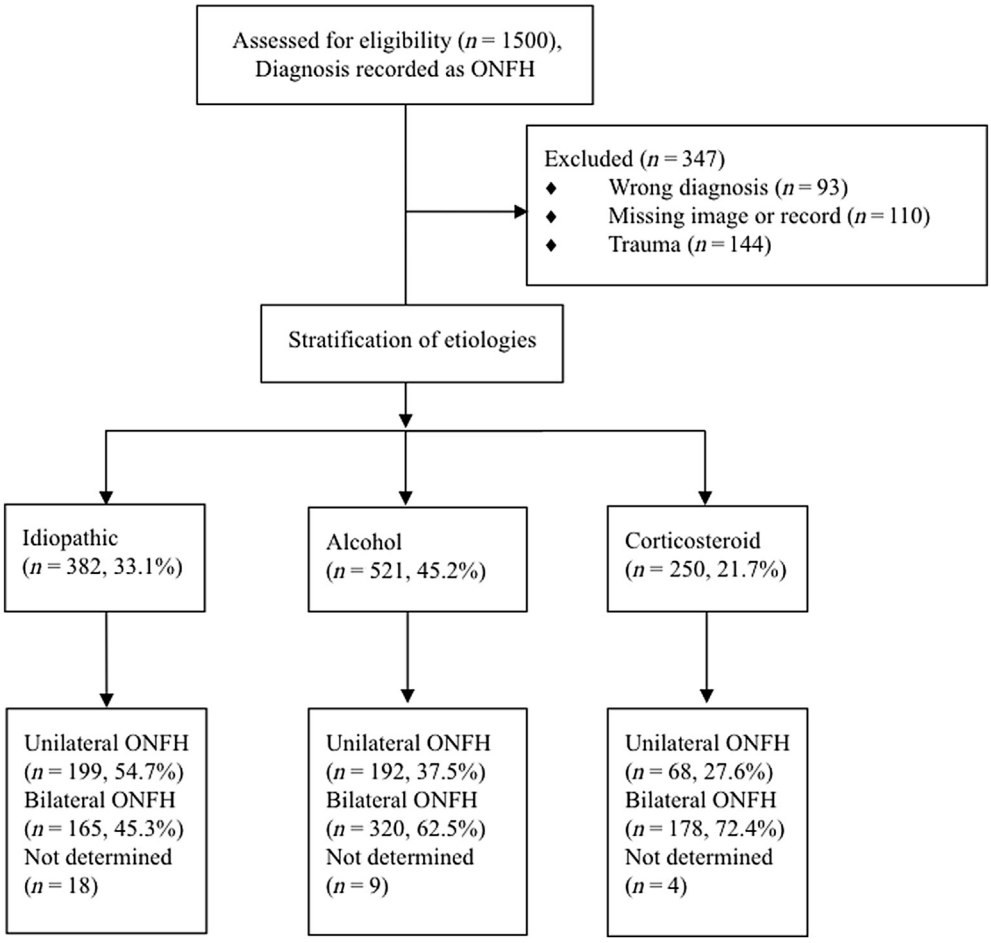

Fig. 1. CONSORT flow diagram detailing the origin of the study cohort. ONFH = osteonecrosis of the femoral head.

Table 1
Indications for corticosteroid in the cohort.

Indications	No. (%)
SLE	109 (43.6)
Hematologic cancer	28 (11.2)
Asthma/COPD	28 (11.2)
Transplantation	16 (6.4)
Nephritic/nephrotic syndrome	11 (4.4)
Intracranial lesion	9 (3.6)
RA	8 (3.2)
Multiple sclerosis	6 (2.4)
Adrenal insufficiency	6 (2.4)
Eczema/urticaria	6 (2.4)
AS	3 (1.2)
Sjögren syndrome	3 (1.2)
Dermatomyositis/polymyositis	3 (1.2)
Psoriasis	3 (1.2)
UC/CD	2 (0.8)
Migraine	2 (0.8)
Iritis	2 (0.8)
Others	5 (2)
Total	250 (100)

AS = ankylosing spondylitis; CD = Crohn's disease; COPD = chronic obstructive pulmonary disease; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; UC = ulcerative colitis.

hip arthroplasty were 44.5 ± 13.7 years and 50.2 ± 14.9 years, respectively. Patients in the corticosteroid group were significantly younger when they had undergone core decompression (38.2 ± 15.0 years) and hip arthroplasty (44.5 ± 17.0 years), compared with those of the alcohol (44.9 ± 10.3 years, 47.8 ± 11.0 years) and idiopathic groups (52.0 ± 13.4 years, 58.6 ± 15.4 years).

The incidence curve of contralateral ONFH is shown in Fig. 2. In idiopathic ONFH, 14.2%, 20.6%, 31.3%, 36.1%, and 43.3% of patients developed contralateral ONFH at 1 year, 2 years, 3 years, 4 years, and 5 years, respectively, after the diagnosis of unilateral ONFH. In alcohol-associated ONFH, 23.4%, 31.7%, 41.5%, 48.3%, and 62.5% of patients developed contralateral ONFH at 1 year, 2 years, 3 years, 4 years, and 5 years, respectively, after the diagnosis of unilateral ONFH. In corticosteroid-associated ONFH, 31.0%, 47.3%, 56.8%, 62.4%, and 66.4% of patients developed contralateral ONFH at 1 year, 2 years, 3 years, 4 years, and 5 years, respectively, after the diagnosis of unilateral ONFH. The incidence of developing contralateral ONFH was significantly higher in corticosteroid- and alcohol-associated ONFH patients than in idiopathic ONFH patients ($p < 0.001$). The mean follow-up time was 2.94 years (range 1 month to 20 years).

Table 2
Demographic data of the study cohort.

	Idiopathic	Alcohol	Steroid	*p*	Total
Sex				<0.001	
Male	208 (26.0)	496 (62.1)	95 (11.9)		799 (69.3)
Female	174 (49.2)	25 (7.1)	155 (43.7)		354 (30.7)
Total					1153 (100)
Height (cm)	160.7 ± 9.4 (136−191) [a]	167.9 ± 6.4 (151−187) [b]	160.0 ± 10.3 (135−182) [a]	<0.001	163.5 ± 9.2 (135−191)
Weight (kg)	64.7 ± 12.1 (34−103) [a]	69.9 ± 12.0 (43−113) [b]	63.3 ± 15.1 (42−107) [a]	<0.001	66.7 ± 12.6 (34−113)
BMI (kg/m^2)	25.0 ± 3.9 (14.4−42.7)	24.8 ± 3.7 (15.8−41.8)	24.7 ± 5.2 (17.3−44.3)	0.604	24.9 ± 4.1 (14.4−44.3)
Core decompression				<0.001	
Number of hips	99	142	113		354
Age at operation (y)	52.0 ± 13.4 (27−83) [a]	44.9 ± 10.3 (23−81) [a]	38.2 ± 15.0 (15−82) [c]		44.5 ± 13.7 (15−83)
Arthroplasty				<0.001	
Number of hips	412	621	287		1320
Age at operation (y)	58.6 ± 15.4 (21−92) [a]	47.8 ± 11.0 (26−88) [b]	44.5 ± 17.0 (15−82) [c]		50.2 ± 14.9 (15−92)

Categorical values are expressed as *n* (%); continuous values are expressed in mean ± standard deviation, with range in parentheses.
[a,b,c] Different letters indicate significant difference across groups.
BMI = body mass index.

The progression of precollapse ONFH was demonstrated (Figs. 3A−3C) in our study patients stratified by etiologies and whether they had undergone core decompression. Overall, patients with corticosteroid- and alcohol-associated ONFH had more rapid progression to postcollapse ONFH ($p = 0.001$). Patients with idiopathic ONFH had slower progression to postcollapse ONFH than those with alcohol- or corticosteroid-associated ONFH who had or had not undergone core decompression ($p = 0.003$ and $p = 0.015$, respectively). Among idiopathic ONFH patients who had not undergone core decompression, 68.7%, 58.4%, 44.4%, 31.3%, and 27.0% remained at precollapse ONFH at 1 year, 2 years, 3 years, 4 years, and 5 years, respectively, after the diagnosis. Among alcohol-associated ONFH patients who had not undergone core decompression, 58.0%, 39.6%, 31.8%, 26.9%, and 24.0% remained at precollapse ONFH at 1 year, 2 years, 3 years, 4 years, and 5 years, respectively, after the diagnosis. Among corticosteroid-associated ONFH patients who had not undergone core decompression, 51.9%, 36.3%, 23.3%, 11.6%, and 1.3% remained at precollapse ONFH at 1 year, 2 years, 3 years, 4 years, and 5 years, respectively, after the diagnosis. Among patients with idiopathic ONFH who had undergone core decompression, 77.0%, 66.2%, 45.1%, 40.7%, and 40.7% were identified with precollapse ONFH at 1 year, 2 years, 3 years, 4 years, and 5 years, respectively, after the diagnosis. Among patients with alcohol-associated ONFH who had undergone core decompression, 56.5%, 33.6%, 30.2%, 26.8%, and 22.1% were found with precollapse ONFH at 1 year, 2 years, 3 years, 4 years, and 5 years, respectively, after the diagnosis. Among patients with corticosteroid-associated ONFH who had undergone core decompression, 56.7%, 46.0%, 30.1%, 30.1%, and 30.1% were found with precollapse

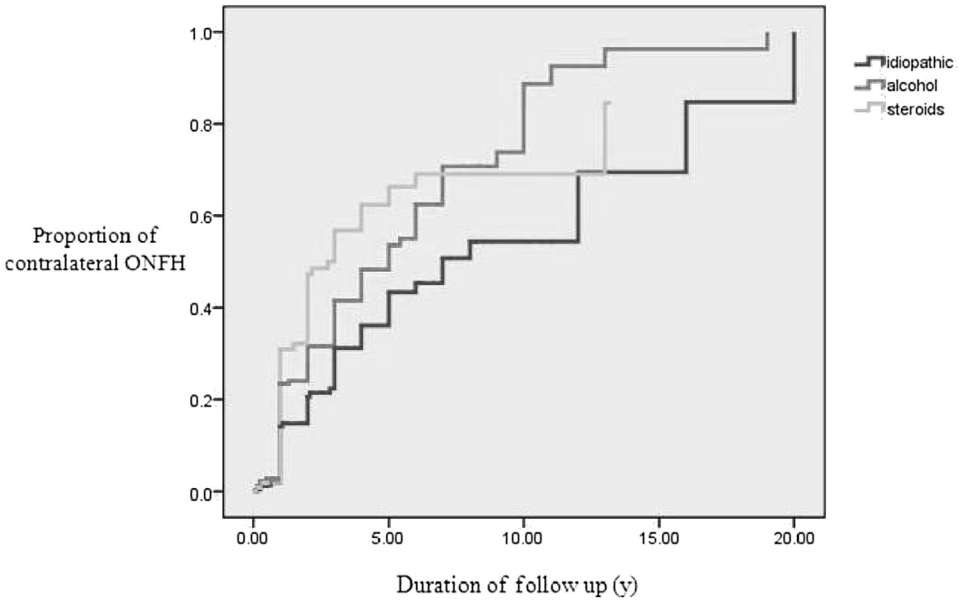

Fig. 2. Incidence curve depicting contralateral osteonecrosis of the femoral head (ONFH; $n = 644$, $p < 0.001$).

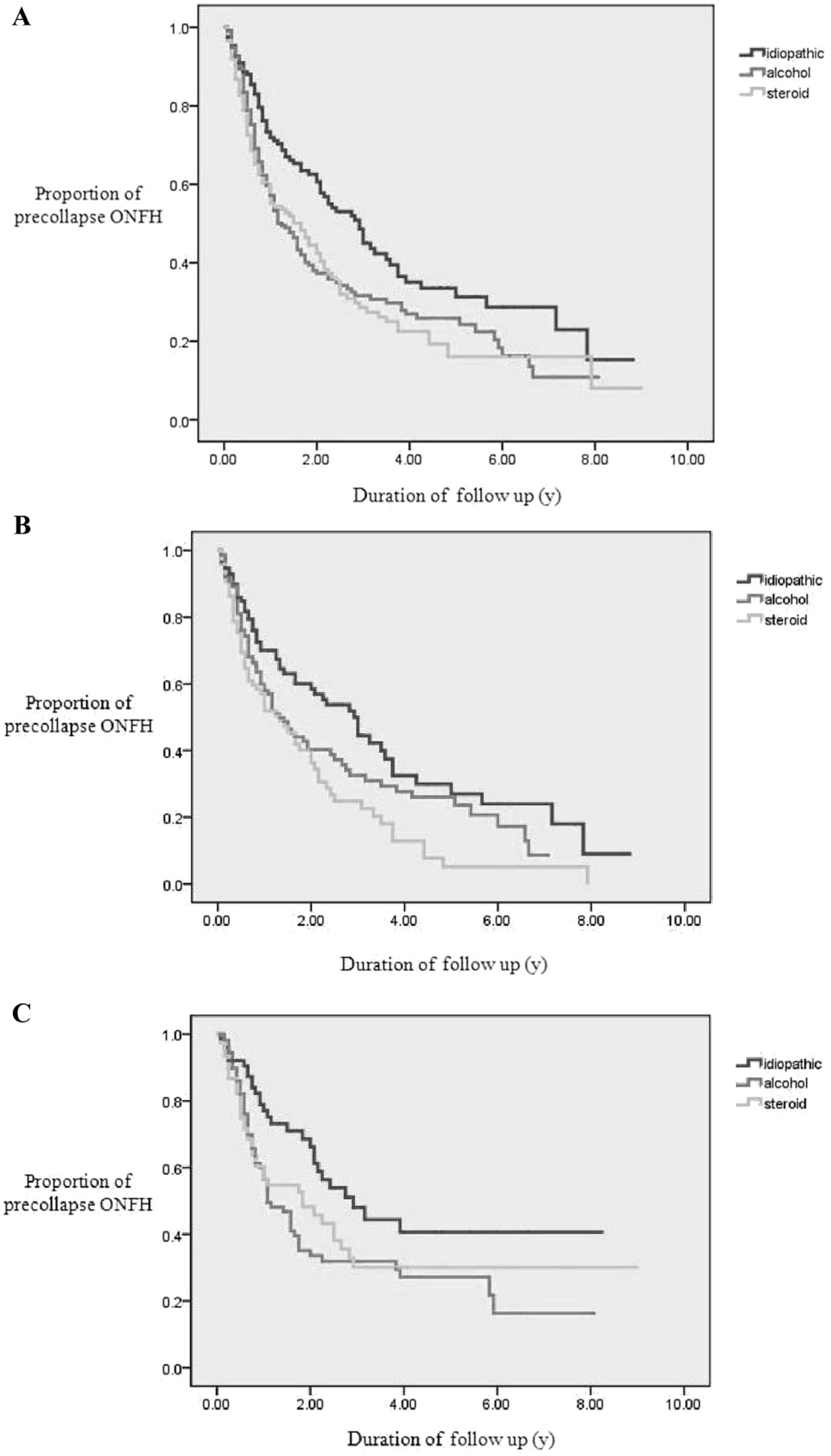

Fig. 3. Kaplan–Meier survivorship curve (based on stratification of etiologies) depicting progression to collapse after the diagnosis: (A) in all patients ($n = 637$, $p = 0.001$); (B) in patients who had not undergone core decompression ($n = 356$, $p = 0.003$); and (C) in patients who had undergone core decompression ($n = 271$, $p = 0.015$). ONFH = osteonecrosis of the femoral head.

ONFH at 1 year, 2 years, 3 years, 4 years, and 5 years, respectively, after the diagnosis. The mean follow-up time was 1.54 years (range 1 month to 9 years).

Steroid and alcohol use were independently associated with worse prognosis of developing contralateral ONFH [hazard ratio (HR) 4.16, 95% confidence interval (CI) 2.06−8.38, $p < 0.001$; HR 1.81, 95% CI 1.12−2.92, $p = 0.016$, respectively] on multivariate analysis. In addition, steroid and alcohol use were independently associated with worse survival of collapse of ipsilateral ONFH (HR 2.01, 95% CI 1.21−3.34, $p = 0.007$; HR 1.45, 95% CI 1.01−2.09, $p = 0.047$, respectively) on multivariate analysis. Core decompression surgery was found to have borderline protective effect against collapse of ipsilateral ONFH (HR 0.743, 95% CI 0.53−1.05, $p = 0.09$). Age, sex, body height, and body weight were not significantly associated with worsened prognosis of developing contralateral ONFH or collapse of ipsilateral ONFH.

4. Discussion

ONFH has been the leading indication for primary THR in Taiwan,[1] which is very different from that reported in Sweden and Norway.[2,3] This major difference illustrates the important impact of ONFH in Taiwan. The etiology of ONFH has been discussed in a Japanese nationwide epidemiologic survey. Systemic corticosteroid and habitual alcohol use accounted for 51% and 31% of ONFH, respectively.[11] A Korean nationwide epidemiology survey reported a history of alcohol and corticosteroid use in 32.4% and 14.6% of ONFH patients, respectively.[12] Castro and Harris[13] reported that corticosteroid and alcohol use accounted for 40.1% and 36.6% of the causes of ONFH, respectively. In our study, the most common etiology of ONFH was alcohol (45.2%). Idiopathic ONFH and corticosteroid-associated ONFH accounted for 33.1% and 21.7%, respectively. Our results were comparable with those of the Korean epidemiology survey but different from those of the Japanese study.[11,12]

Alcohol and corticosteroid use have been reported to be risk factors of ONFH.[11,13−17] The average ages at which corticosteroid-associated ONFH patients had undergone core decompression and hip arthroplasty were 38.2 years and 44.5 years, respectively. Corticosteroid-associated ONFH patients were younger when they received core decompression and hip arthroplasty, compared with those in the alcohol (44.9 years and 47.8 years) and idiopathic groups (52.0 years and 58.6 years). Castro and Harris[13] reported that the onset of ONFH in the corticosteroid, alcohol, and idiopathic groups was at 39 years, 49 years, and 42 years, respectively. Jacobs[18] also demonstrated that alcohol-associated ONFH patients had an average duration of alcohol abuse of 9.5 years. In that study, 28% of the patients were aged < 40 years and 76% were aged < 50 years. ONFH has been reported to be an important morbidity in the SLE population, with prevalence ranging from 10.14% to 52%.[16,19−22] Among our corticosteroid-associated ONFH patients, SLE accounted for 43.6% (109 patients). The average age for SLE patients to undergo core decompression and hip arthroplasty was 35.54 years and 36.79 years, respectively. SLE accounted for the largest proportion of this group, and the patients were much younger.

Alcohol was the most prevalent etiology of ONFH in our population. Average daily amount of alcohol consumption was 86.2 g. It is interesting that there was a great male predominance (95.2%) among alcohol users. Further studies are necessary to figure out whether this predominance was because of the different proportion of habitual alcohol consumption between sexes or a possible protective mechanism in females against exposure to alcohol.

The overall proportion of bilateral ONFH was 59.1%. The proportion of bilateral disease was 72.4% in corticosteroid-associated ONFH patients, which is higher than the proportions in patients with alcohol-associated ONFH (62.5%) and idiopathic ONFH (45.3%). The proportion of bilateral ONFH varied from 47% to 78.3% in different populations indicated for corticosteroid use.[15−17,23] Castro and Harris[13] reported 49%, 40%, and 35% of bilateral disease at initial presentation in corticosteroid-associated, alcohol-associated, and idiopathic ONFH, respectively.[13] We had subsequent follow up in all patients, which might have led to the increase in the proportion in all etiologies.

Various factors have been reported to increase the risk of progress to postcollapse ONFH, including initial stage,[6] lesion location,[4,7−9] lesion size,[4,5,7−9] and sickle cell anemia.[6] We described the difference in outcome among etiologies. In our findings, among the study groups, there was a significant difference in the survival rate of precollapse ONFH patients who did or did not receive core decompression. The initial stages were not different between etiologies. Worse outcome was noted in corticosteroid- and alcohol-associated ONFH than in idiopathic ONFH. The 5-year survival rates were 27.0%, 24.0%, and 1.3%, respectively, in patients with idiopathic, alcohol-associated, and corticosteroid-associated ONFH who had not undergone core decompression. In patients who had undergone core decompression, the 5-year survival rates was 40.7%, 22.1%, and 30.1%, respectively, in idiopathic, alcohol-associated, and corticosteroid-associated ONFH. In our study, no other conservative or surgical treatment except for core decompression without bone grafting or with nonvascularized trochanteric bone graft was performed. Persistent exposure to irritants in these patients as a necessity for corticosteroid treatment in case of diseases or alcohol addiction might lead to inferior outcome than in patients without such exposure.

According to our study, ONFH presents frequently bilaterally, especially in alcohol and corticosteroid users. It was possible to detect early contralateral disease when patients presented initially with unilateral ONFH. No study has demonstrated the incidence of contralateral ONFH among etiologies. Goker and Block[10] reported that initial positive radiographic evidence of contralateral hip was likely to correlate with subsequent progress of the disease after ipsilateral THR. In addition, the author stated that asymptomatic contralateral hip without radiographic evidence was not likely to progress to symptomatic ONFH.[10] In the 663 patients with bilateral ONFH in our study, 215 patients (32.4%) were

asymptomatic and without initial radiographic evidence of contralateral hip but developed subsequent contralateral ONFH during the follow up. In addition, the proportion at the 5th year was higher in corticosteroid-associated ONFH (66.4%) and alcohol-associated ONFH (62.5%) than in idiopathic ONFH (43.3%). Therefore, awareness of contralateral early ONFH is important in patients presenting with unilateral ONFH, especially in alcohol- and corticosteroid-associated ONFH patients.

This study has several limitations. First, this was a retrospective study. Second, MRI was not available for all the patients during the follow up. For precollapse ONFH, the end point was defined as collapse of the femoral head. This should be adequately detected using plain films. However, it would be expected to miss cases with contralateral Stage I ONFH if MRI was not used as a screening tool. The true incidence of contralateral ONFH should be higher. Third, the follow-up period was relatively short (2.94 ± 2.75 years). Although the collapse occurred mostly within the first few years following the initial diagnosis, the survival curve of the longer term might not be as accurate as the shorter term. Fourth, we defined idiopathic ONFH by exclusion of alcohol- and corticosteroid-associated ONFH. It should be recognized that potential misclassification could occur even though the other etiologies were extremely rare or had less impact compared with alcohol and corticosteroid use. Finally, although we attempted to improve the reliability of the definition of alcohol- and corticosteroid-associated ONFH by documentation of average daily alcohol consumption and indication of corticosteroid use, this definition is still insufficient. However, exact dose and duration of alcohol and steroid use that leads to ONFH has not yet been established.

In conclusion, alcohol had the greatest impact on ONFH in our population. Patients who had corticosteroid or alcohol use had earlier onset and bilateral disease, a higher rate of disease progression, and onset of contralateral disease. Understanding the disease nature of ONFH may provide great prognostic value to detect and perform early intervention.

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