# Prevalence and risk factors of hepatocellular carcinoma in Japanese patients with primary biliary cirrhosis



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**Review article**

# Prevalence and risk factors of hepatocellular carcinoma in Japanese patients with primary biliary cirrhosis

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**ABSTRACT**

Primary biliary cirrhosis (PBC) tends to affect females more than males. PBC selectively damages intrahepatic small bile ducts, particularly interlobular bile ducts. The clinical presentation of PBC has changed according to recent advances in clinicobiological diagnosis and improvements in therapeutic effects and prognosis. In particular, we encounter PBC patients with hepatocellular carcinoma (HCC), and the number of these patients appears to have increased. The precise reason for the increased number of PBC patients with HCC in recent decades remains unknown, but recognizing the current status of carcinogenesis in PBC patients, identifying the associated clinicopathological risk factors, and understanding how the pathogenesis of PBC is directly associated with HCC, is important. In this review, we summarize the data from two nationwide surveys undertaken in Japan as well as recent data from Japanese and international studies.

Key Words: primary biliary cirrhosis, hepatocellular carcinoma, gender, carcinogenesis

## INTRODUCTION

Primary biliary cirrhosis (PBC) is an autoimmune liver disease. It tends to affect females more than males. PBC selectively damages the intrahepatic small bile ducts, particularly interlobular bile ducts. Because of progressive loss of bile ducts, PBC develops into chronic cholestasis and finally biliary cirrhosis.

The clinical presentation of PBC has been changing over the years. In particular, the proportion of asymptomatic patients at diagnosis has increased. In contrast to other primary biliary diseases such as primary sclerosing cholangitis (PSC), the associated malignant tumor of PBC is hepatocellular carcinoma (HCC), although its incidence is low. The detailed clinicopathological significance and carcinogenesis of HCC associated with PBC remain unknown. In this review, recent data from Japan[1] and other countries are reviewed.

### Complication of malignancy in patients with PBC

Several studies have indicated that PBC may be associated with an increased risk of extrahepatic malignancies as well as HCC, although they represent a rare complication. By surveying 212 Greek patients with PBC, 10.8% patients were diagnosed with malignancy, 3.8% patients with HCC, and 7.0% with extrahepatic malignancies.[2] Moreover, a meta-analysis using PubMed and EMBASE databases revealed that PBC is closely associated with a greater risk of overall cancer and HCC, but not with other cancers.[3] With respect to HCC, its incidence in patients with PBC varies from 0.76% to 5.9% depending on reports.[2, 4-9] However, one report has stated that PBC is not risk factor for HCC.[10] These divergent results may be because of the low prevalence of the association with HCC as well as geographical and environmental

differences. However, the number of PBC patients associated with HCC has been recently increased, which might be due to the improvement of therapeutic effects and prognosis.[11-13]

National surveys of patients with PBC in Japan have been undertaken 15 times biennially or triennially by the Intractable Hepato-Biliary Diseases Study Group for Research on Measures for Intractable Disease, which is supported by Health Labor Sciences Research Grants in Japan. The surveys involved 8509 patients registered in the 1st–15th surveys performed between 1980 and 2012.[9, 14, 15] According to the 15th National Survey performed in 2012, the incidence of malignancy at the time of PBC diagnosis was 3.3%. Liver cancer was the most common (24%), followed by gastric cancer (16%), colon cancer (12%), breast cancer (10%), uterine cancer (5%), thyroid cancer (6%), hematopoietic cancer (5%), ovarian cancer (3%), lung cancer (3%), and others (16%) [15].

**Risk factors for HCC in patients with PBC based on data from Japan and other countries**

According to epidemiological studies by single and multiple centers, cirrhosis, portal hypertension, advanced age, diabetes mellitus (DM), being male, blood transfusion, smoking, and excessive intake of alcohol are reported as risk factors for HCC (in addition to infection by the hepatitis virus), but these risk factors vary among reports.[4-7, 12, 16-18] Moreover, cases of patients with HCC arising from patients with non-cirrhotic PBC have been reported, and consideration of the carcinogenesis of HCC in PBC was noted. The Japanese data reported by Shibuya et al.[6] highlighted the importance of age at the time of PBC diagnosis, male sex, and history of blood

transfusion as independent risk factors associated with the development of HCC by proportional hazards analyses. In general, autoimmune diseases (including PBC), irrespective of the organs affected, preferably affect females more than males, but the incidence of HCC in PBC and autoimmune hepatitis (AIH) is higher in males than in females.[13] This difference in incidence between the sexes has been reported and confirmed in studies outside Japan.[6, 7, 12, 17, 18].

**National survey of PBC with HCC in Japan**

According to the 14th National Survey among patients with PBC with HCC in Japan, undertaken in 2009 among 2946 subjects (70 males, 2576 females) confirmed to either have or not have HCC as well as exclusion of hepatitis-B virus (HBV) carriers and HB antigen- and anti-hepatitis-C virus (HCV) antibody-positive patients, the incidence of HCC during follow-up was 2.4% (71/2946). This incidence was 5.1% (19/370) in males and 2.0% (52/2576) in females, and the proportion of males was 26.7%.[1, 19] Moreover, according to a cohort study by the National Hospital Organization Study Group for Liver Disease in Japan, 20 cases (2.0%) (male/female = 5/15; proportion of males, 25%) among the 1007 patients with PBC registered in 1989–2011 had HCC,[20] supporting a similar value for the incidence revealed by the National Survey of PBC in Japan. Therefore, in Japan, the incidence of HCC in patients with PBC and the proportion of males have been speculated to be 2% and 25%, respectively. Although the incidence of HCC is low, the incidence and mortality in patients with PBC are significantly higher than those in the general population of Japan based on detail analyses using the standardized incidence ratio and standardized mortality ratio (SMR) of HCC in patients with PBC.[21].

According to a comparative analysis of this population obtained from the National Surveys of patients with PBC in Japan (2009), male sex, old age, low serum albumin levels, low serum total cholesterol levels, advanced histological stage, and symptomatic status at the time of PBC diagnosis were significant risk factors for HCC (Table 1)[1, 22]. The cumulative incidence of carcinogenesis was 6.5% in males and 2.0% in females during the 10 years after PBC diagnosis; the difference between males and females was statistically significant (Fig. 1). In particular, analyses of the incidence of HCC in patients aged 10–80 years revealed that male patients with PBC in their forties and fifties had an increased risk of HCC compared with female patients with PBC in the same age groups. In multivariate analyses for risk factors of HCC, sex and histological stage were selected as the only significant factors among male sex, old age, low serum albumin levels, low serum total cholesterol levels, advanced histological stage, and symptomatic status raised by comparative analyses. By multivariate analyses for risk factors of HCC by sex, histological stage at the time of PBC diagnosis was an independent risk factor for HCC in females (Table 2), whereas no significant independent factors were selected in males (Table 3). With respect to histological stage, there was no difference in the proportion of males and females who underwent histological staging at the time of PBC diagnosis (Fig. 2). The incidence of histological stages 3 and 4 was approximately 16.0% in male and female patients with PBC without HCC (Fig. 2), whereas it was 14.2% and 57.1% in male and female patients with PBC with HCC, respectively.[1, 22] Advanced histological stage was a risk factor for HCC in females but not in males (Fig. 2, Tables 2 and 3). Therefore, male patients with PBC should be followed-up to consider the possibility of complication with HCC in any PBC stage.

**Survey of patients with PBC with HCC in Japan**

At the 47th Annual Meeting of the Liver Cancer Study Group of Japan, the survey of 178 patients with PBC with HCC (100 fatalities in the past years and 78 patients followed-up) revealed that the proportion of males was 27.5% (49 males and 129 females), which was similar to that from the National Survey of PBC in Japan. The average age at the time of PBC diagnosis was higher for males (68 years) than for females (62 years), but the time of HCC diagnosis was similar between males (73 years) and females (72 years; Fig. 3). Moreover, the duration between the diagnosis of PBC and that of HCC was shorter in males than in females (Fig. 3). HCC was simultaneously diagnosed during or before PBC diagnosis in 32.7% (16/49) males and 14.7% (19/129) females.

Clinicopathological data at the time of HCC diagnosis are shown in Table 4. There were more males with previous HBV infection and a history of alcohol consumption than females. There were no differences with respect to the history of blood transfusion, diabetes mellitus, apical membrane antigen levels, antinuclear antibody levels, body mass index, serum triglyceride levels, serum total cholesterol levels associated with nonalcoholic fatty liver disease (including nonalcoholic steatohepatitis), and use of ursodeoxycholic acid (UDCA; Table 4) between males and females. However, an analysis excluding patients with previous HBV infection and a history of alcohol consumption revealed no difference in other clinical findings, although the proportion of males (male/female = 24/104, 18.5%) remained higher than that of the male patients with PBC (male/female = 370/2576, 12.6%). Moreover, in females, the incidence of HCC gradually increased with the histological stage, whereas

that in males showed no trend or statistical significance. There was a significant difference in the distribution of the histological stage between males and females (Fig. 4). An analysis of patients with PBC with HCC according to the histological stage revealed no clinical findings (including previous HBV infection and alcohol consumption) that were significantly different between patients with and without cirrhosis at the time of HCC diagnosis, suggesting that previous HBV infection and alcohol consumption are not directly associated with progression to cirrhosis in patients with PBC with HCC.

**Pathology of HCC in patients with PBC**

With regard to the pathological findings of HCC, approximately two-thirds of patients showed a solitary mass, and there was no difference in sex according to the National Survey at the 47th Annual Meeting of the Liver Cancer Study Group of Japan. The degree of differentiation in HCC was mostly well-differentiated and moderately differentiated, and there was no difference in sex. Therefore, the risk factors and carcinogenesis of HCC differ between males and females, but the features of complicated HCC are common between males and females (Table 5). As notable pathological findings, a survey of Japanese autopsy cases of PBC disclosed that fatty changes or bile plugs within tumors were frequently observed.[23] Mallory body clusters and focal copper-binding protein deposition were consistently found in cirrhotic liver and carcinoma tissues. Moreover, HCC in patients with PBC was speculated to evolve through multiple steps because of the presence of dysplastic nodules in the peripheries of liver tissues.[23]

## Carcinogenesis of HCC and its risk factors

**Why does HCC develop in patients with PBC?** PBC and PSC are typical biliary inflammatory diseases. PSC is a precursor lesion of cholangiocarcinoma, although based on the national survey in 2003,[24] its incidence is relatively low in Japan (3.6%) compared with that in Europe and USA (7%–15%).[25] In contrast, HCC is the associated malignancy with PBC (but not cholangiocarcinoma), even though the etiology and carcinogenesis of HCC associated with PBC remain unknown. In PBC, hepatic changes as well as cholangitis are involved in its pathogenesis.[26] However, this hepatic activity causing hepatocellular damage is speculated to be involved in the carcinogenesis of HCC in patients with PBC. Differing from the direct hepatocellular damage associated with virus and autoimmune reactions found in viral and autoimmune hepatitis, hepatocellular damage associated with chronic cholestasis and chronic inflammation (including interface hepatitis) may be associated with carcinogenesis of HCC in patients with PBC. In PBC, chronic cholestasis occurs from an early stage of PBC, and mitogenic factors in the bile could be directly associated with PBC carcinogenesis.[11, 23, 27, 28]

## Cirrhosis

The incidence and mortality rate of HCC in Japanese patients with PBC are significantly higher than those in the general Japanese population.[21] However, in patients with cirrhosis, the risk is considerably higher in PBC, and cirrhosis could be a risk factor of HCC irrespective of their etiologies. In Japan, PBC as an etiology of cirrhosis is observed in 2.4% cases.[29] In the cirrhotic state, stress to the hepatocytes could be associated with HCC carcinogenesis. Moreover, most

female patients with PBC with HCC develop the advanced stage (including cirrhosis) at the time of HCC diagnosis (Fig. 3), supporting several reports stating that cirrhosis is a risk factor for HCC.[6, 7, 17, 18] In contrast, Kuiper et al. [30] reported on the possibility that UDCA may protect against HCC. In UDCA-treated patients with PBC, the risk of HCC was relatively low, but the main risk factor for HCC was the absence of a biochemical response to UDCA and the development of cirrhosis. However, compared with females, the proportion of males with PBC with HCC was almost equally distributed among stages 1–4 (Fig. 4), suggesting a male-specific risk factor.

**Males**

PBC affects females more than males, but the rate of carcinogenesis is higher in males than in females. However, the male-predominance of HCC is not exclusive to PBC, and is a common risk factor for developing HCC irrespective of its etiology. The reason for the rate of carcinogenesis being higher in males is speculated be because of the inhibitory mechanism of estrogen in the carcinogenesis of HCC. The inflammatory cytokine interleukin (IL)-6 is produced by Kupffer cells and is associated with constitutive damage and malignant transformation of hepatocytes in the development of HCC. During this HCC carcinogenesis, estrogen inhibits the development of HCC by attenuating the IL-6 production from Kupffer cells.[31, 32] Therefore, PBC affects females more than males, but with respect to the carcinogenesis of HCC, the estrogen deficiency-related HCC carcinogenesis is speculated to be closely associated with the high incidence of HCC in males.

**Previous HBV infection and excessive alcohol intake**

According to the 47th Annual Meeting of the Liver Cancer Study Group of Japan (2011), the time from the diagnosis of PBC to that of HCC is shorter in males than in females (Fig. 3). Moreover, the proportion of patients simultaneously diagnosed with PBC and HCC and with HCC before PBC was 32.7% in males and 14.7% in females, and the ratio of these cases in males was significantly higher than that in females (Fig. 3)[1]. The reason for this significant difference is not because of the late diagnosis or underdiagnosis of HCC in males but because of the development of HCC from an early stage of PBC in males (Fig. 4). Moreover, the ratio of males with a history of HBV infection and excessive intake of alcohol was significantly higher than that of females (Table 4), suggesting that these risk factors could be associated with HCC carcinogenesis during the early stages in male patients with PBC. However, statistical analysis excluding these patients with these risk factors revealed that the incidence of HCC in males remained higher than that in females, suggesting that the male gender was not a confounding factor. Moreover, the ratio of previous HBV infection and excessive intake of alcohol was not significantly different between cirrhotic (Scheuer stage 4) and non-cirrhotic (Scheuer stages 1–3) patients, suggesting that at least these two factors are not associated with the development of cirrhosis in PBC patients with HCC.[1] Among patients with a previous HBV infection, integration of the HBV gene into the human genome has been reported to be associated with HCC carcinogenesis,[13] but the frequency and incidence of these patients among patients with PBC patients with HCC is not known.

**Conclusion**

The difference between the sexes with regard to the association of HCC

among patients with PBC is an important risk factor in the HCC carcinogenesis in patients with PBC. However, it is not clear if HCC carcinogenesis is a specific mechanism for PBC. Moreover, in females, the development of cirrhosis is a risk factor for HCC in PBC. In males, HCC cases arising from an early PBC stage are not rare. Hence, male patients with PBC should be carefully followed-up from an early stage to identify HCC.

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Figure legends

Fig. 1. Cumulative rates for appearance of hepatocellular carcinoma (HCC) in patients with primary biliary cirrhosis (PBC) according to sex. There is a statistically significant difference between males and females.

Fig. 2. Histological stage of patients with primary biliary cirrhosis (PBC) with or without hepatocellular carcinoma (HCC) according to sex. There is a significant difference in the proportion of female primary biliary cirrhosis (PBC) patients with HCC and those without.

Fig. 3. Average age at the time of diagnosis of primary biliary cirrhosis (PBC) and hepatocellular carcinoma (HCC), and the duration between the diagnosis of PBC and that of HCC. The duration between the diagnosis of PBC and that of HCC is shorter in males than in females.

Fig. 4. Histological stage according to sex at the time of hepatocellular carcinoma (HCC) diagnosis in patients with primary biliary cirrhosis (PBC). In females, the incidence of HCC gradually increases according to the histological stage, with a statistically significant difference.

**Table 1** **Clinical characteristics of patients with primary biliary cirrhosis (PBC) with or without hepatocellular carcinoma (HCC) at the time of PBC diagnosis (comparative analysis)**

| | HCC (+) | HCC (−) | p |
|---|---|---|---|
| Case number | 71 | 2875 | |
| Sex (M:F)* | 19:52 | 351:2524 | 0.0003 |
| Age (mean ±SD) | 60.5 ± 10.4 | 56.4 ± 11.2 | 0.0023 |
| T-Bilirubin (mean ± SD) | 1.37 ± 1.63 | 0.99 ± 1.52 | 0.1061 |
| Albumin (mean ± SD) | 3.81 ± 0.58 | 4.05 ± 0.51 | 0.0002 |
| T-cholesterol (mean ± SD) | 201.3 ± 60.5 | 217.4 ± 86.7 | 0.0397 |
| Histological stage* (I/II/III/IV) | 10/17/14/8 | 1060/662/263/66 | <0.0001 |
| Use of UDCA (%) | 89.7 | 91.8 | 0.5291 |
| Clinical stage (asymptomatic:symptomatic) | 38:33 | 2775/100 | <0.0001 |

Underlines denote statistically significant items. *These are also selected as risk factors of HCC by multivariate analyses

# Table 2

**Factors associated with the risk of hepatocellular carcinoma (HCC) at the time of primary biliary cirrhosis (PBC) diagnosis in female patients with PBC (multivariate analyses)**

| | Regression coefficient | Standard deviation | $\chi^2$ | Odds ratio | P |
|---|---|---|---|---|---|
| Age | −0.0130 | 0.0174 | 0.56 | 0.9870 | 0.4531 |
| T-Bilirubin | 0.0817 | 0.1171 | 0.49 | 1.0851 | 0.4852 |
| Albumin | −0.1771 | 0.3366 | 0.28 | 0.8376 | 0.5987 |
| T-cholesterol | 0.0038 | 0.0033 | 1.32 | 1.0038 | 0.2512 |
| Histological stage (I/II/III/IV) | −1.0255 | 0.1964 | 27.25 | 0.3586 | <0.0001 |
| Use of UDCA (%) | −0.1607 | 0.3151 | 0.26 | 1.3791 | 0.6100 |
| Clinical stage (asymptomatic:symptomatic) | 0.4252 | 0.1913 | 4.94 | 0.4271 | 0.0263 |

Underlines denote statistically significant items

# Table 3

**Factors associated with risk of hepatocellular carcinoma (HCC) at the time of primary biliary cirrhosis (PBC) diagnosis in male patients with PBC (multivariate analyses)**

| | Regression coefficient | Standard deviation | $\chi^2$ | Odds ratio | P |
|---|---|---|---|---|---|
| Age | −0.0542 | 0.0319 | 2.89 | 0.9472 | 0.0893 |
| T-Bilirubin | −0.1018 | 0.1790 | 0.32 | 0.9032 | 0.5697 |
| Albumin | 0.5884 | 0.5591 | 1.11 | 1.8011 | 0.2926 |
| T-cholesterol | 0.0001 | 0.0020 | 0.00 | 1.0001 | 0.9511 |
| Histological stage (I/II/III/IV) | 0.2484 | 0.4096 | 0.37 | 1.2819 | 0.5443 |
| Use of UDCA (%) | −0.5367 | 0.4254 | 1.59 | 2.9258 | 0.2071 |
| Clinical stage (asymptomatic:symptomatic) | −0.3590 | 0.4635 | 0.60 | 2.0506 | 0.4385 |

**Table 4**

**Clinical characteristics of patients with primary biliary cirrhosis (PBC)at the time of hepatocellular carcinoma (HCC) diagnosis**

| | Male (n = 49) | Female (n = 129) | Total (n = 178) |
|---|---|---|---|
| Blood transfusion | 9% | 8% | 9% |
| Past HBV infection* | 33% | 18% | 22% |
| Alcohol intake* | 27% | 2% | 9% |
| Diabetes mellitus | 24% | 23% | 24% |
| AMA level | 86% | 82% | 83% |
| ANA level | 41% | 49% | 47% |
| BMI (≥25%) | 25% | 31% | 29% |
| Triglyceride (≥150) | 8% | 9% | 9% |
| Total cholesterol (>220) | 15% | 9% | 11% |
| associated with NAFLD | 0% | 4% | 3% |
| Use of UDCA | 84% | 84% | 84% |

Underlines denote statistically significant items. *$p < 0.05$

Table 5

**Pathological characteristics of hepatocellular carcinoma (HCC) in patients with primary biliary cirrhosis (PBC) with HCC**

| | Male | Female | Total |
|---|---|---|---|
| Number of HCC | (n = 49) | (n = 128) | (n = 178) |
| Solitary | 65% | 60% | 62% |
| Multiple | 35% | 38% | 37% |
| Unknown | 0% | 2% | 2% |
| Differentiation of HCC | (n = 25) | (n = 41) | (n = 66) |
| Well | 44% | 37% | 39% |
| Moderately | 48% | 56% | 53% |
| Poorly | 8% | 7% | 8% |

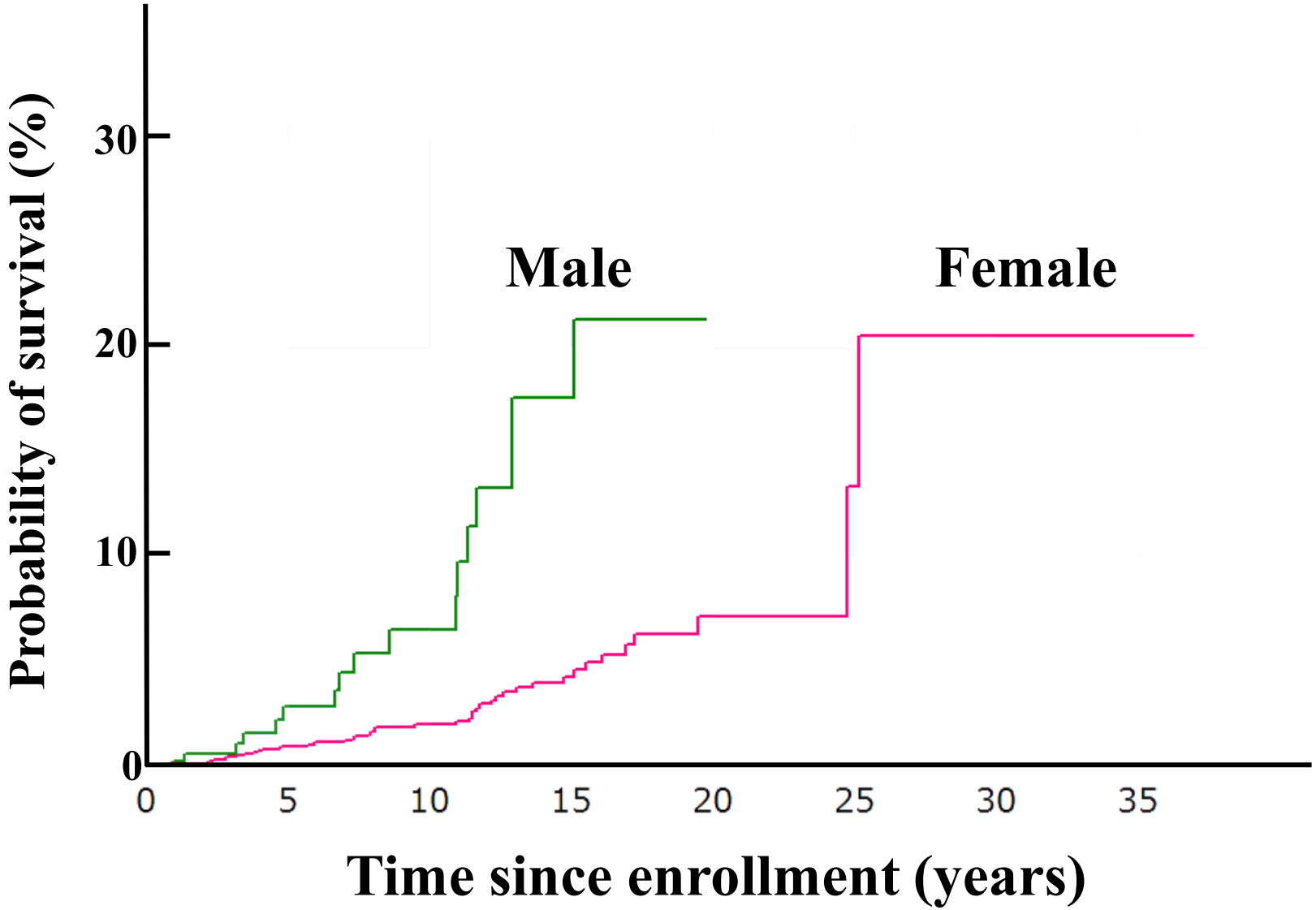

Probability of survival (%)
30
20
10
0
Male
Female
0
5
10
15
20
25
30
35
Time since enrollment (years)

Fig. 1

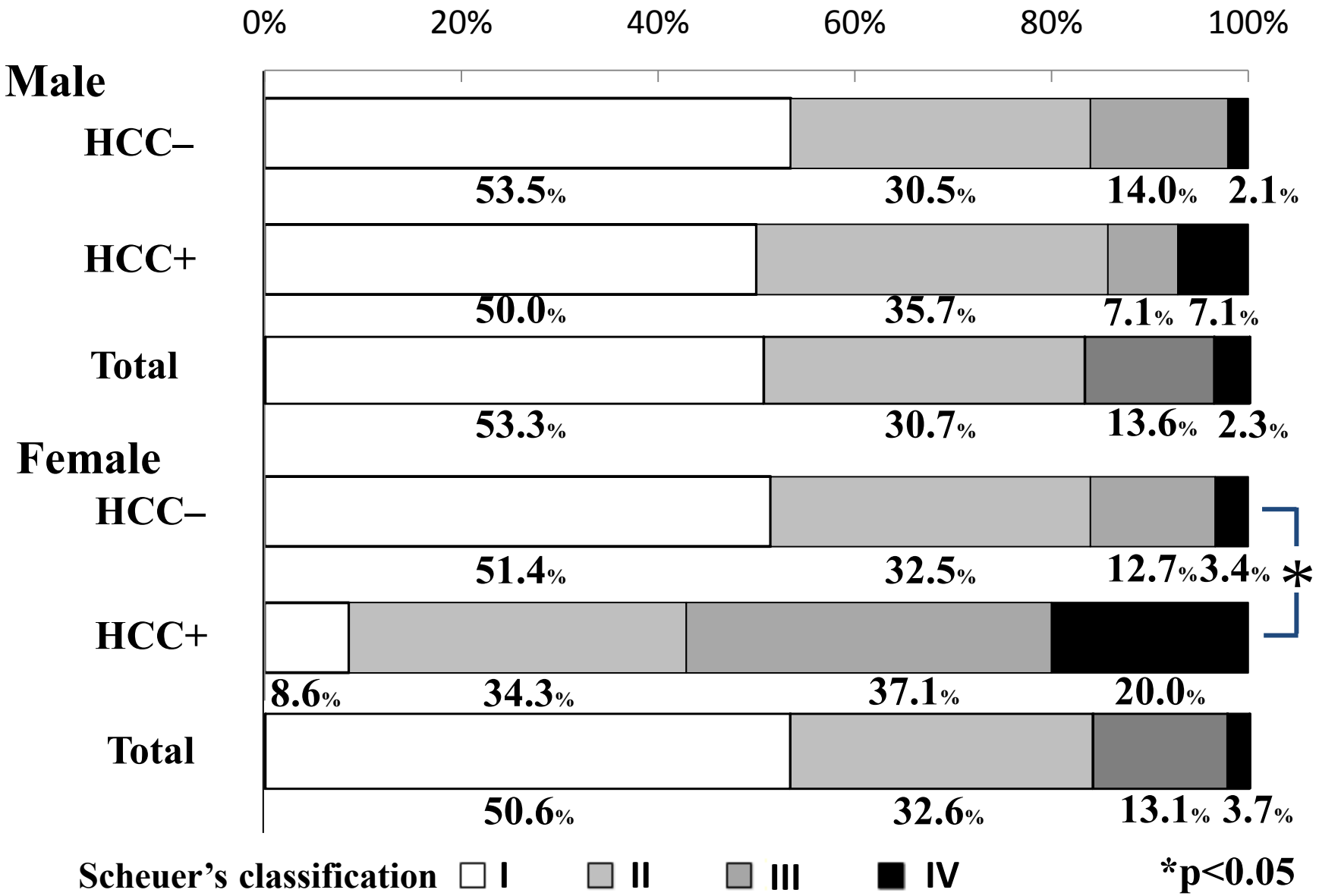
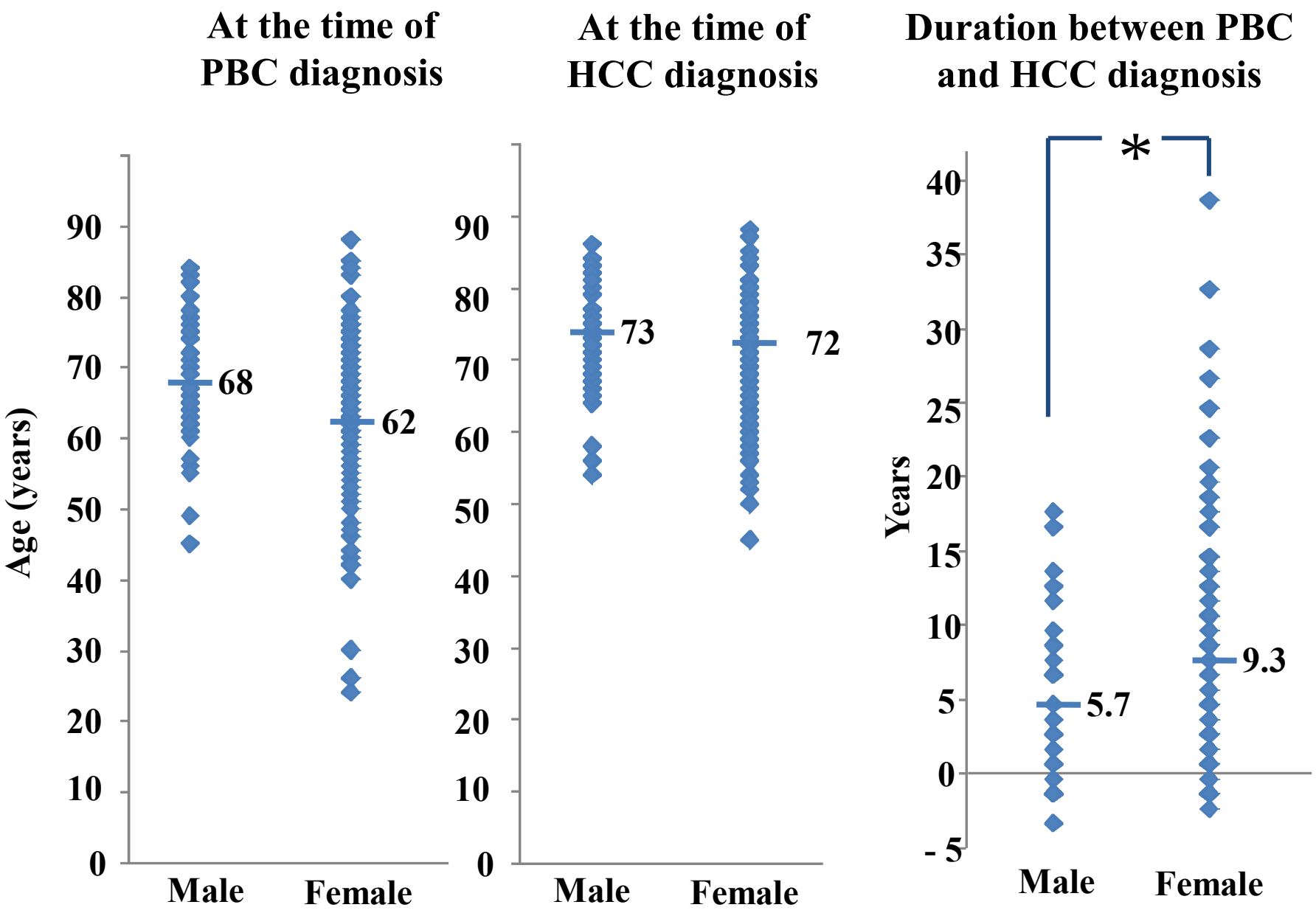

0%
20%
40%
60%
80%
100%
Male
HCC–
53.5%
30.5%
14.0%
2.1%
HCC+
50.0%
35.7%
7.1%
7.1%
Total
53.3%
30.7%
13.6%
2.3%
Female
HCC–
51.4%
32.5%
12.7%
3.4%
*
HCC+
8.6%
34.3%
37.1%
20.0%
Total
50.6%
32.6%
13.1%
3.7%
Scheuer's classification
I
II
III
IV
*p<0.05

Fig. 2


At the time of PBC diagnosis
At the time of HCC diagnosis
Duration between PBC and HCC diagnosis
Age (years)
Years
90
80
70
60
50
40
30
20
10
0
68
62
73
72
40
35
30
25
20
15
10
5
0
- 5
5.7
9.3
*
Male
Female
Male
Female
Male
Female

(*p<0.05)

Fig. 3

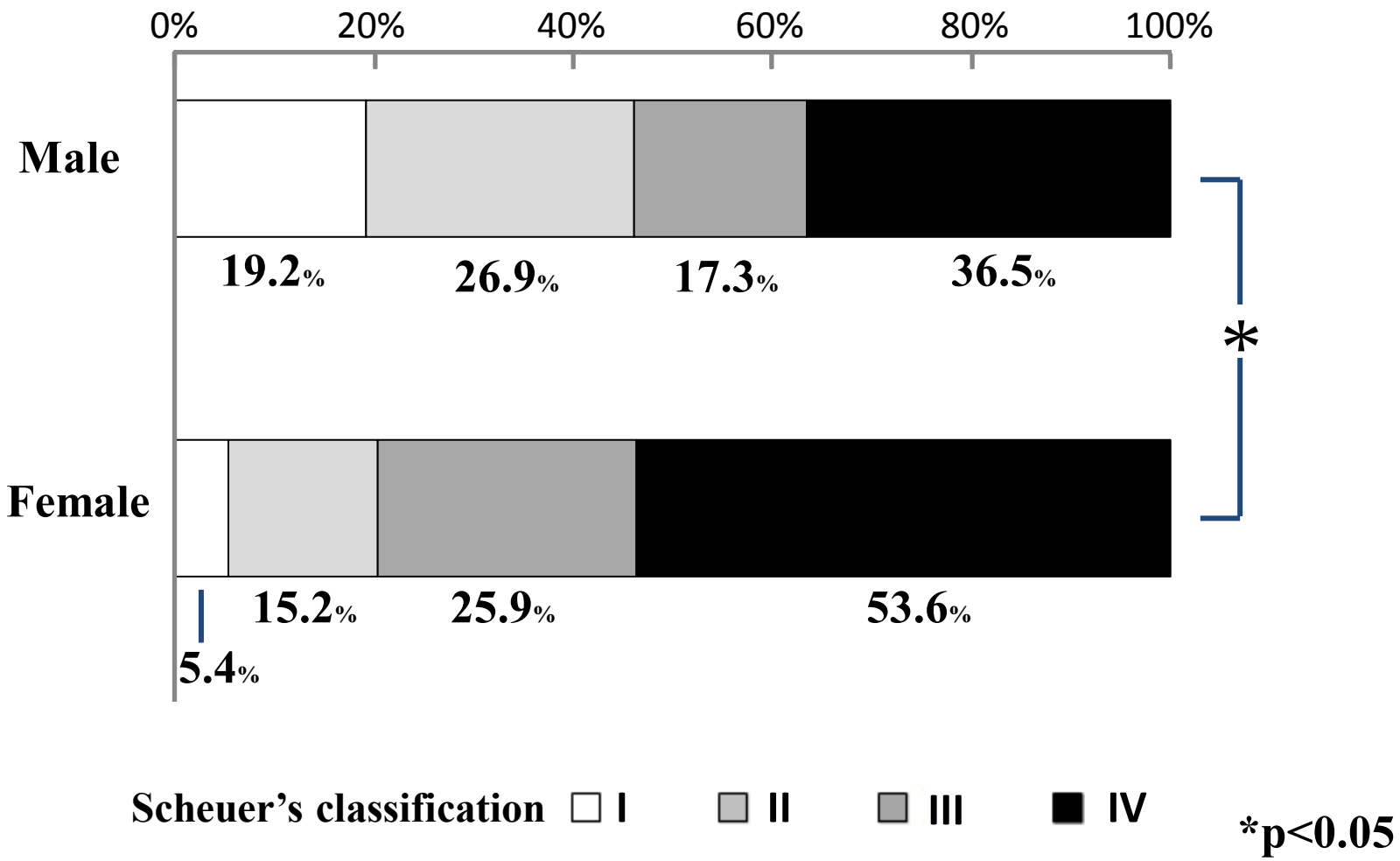

0%
20%
40%
60%
80%
100%
Male
19.2%
26.9%
17.3%
36.5%
*
Female
5.4%
15.2%
25.9%
53.6%
Scheuer's classification
I
II
III
IV
*p<0.05

Fig. 4