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ORIGINAL ARTICLE

The Clinicopathologic Significance of BAF250a (ARID1A) Expression in Hepatocellular Carcinoma

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Abstract Hepatocellular carcinoma (HCC) is one of the most common and lethal human cancers. Recently, exome sequencing has revealed that mutation of *ARID1A* is frequent in HCC. Herein, we determined the clinicopathologic significance of ARID1A expression in HCC. We detected the level of mRNA and protein expression of *ARID1A* in 12 paired HCC tumors and adjacent non-cancerous tissues by quantitative real-time PCR and immunohistochemistry (IHC). In addition, we determined the expression of BAF250a on 121 HCC tumors by IHC and assessed the association between BAF250a expression and clinicopathologic and prognostic features. The levels of *ARID1A* mRNA were significantly elevated in 10 of 12 HCC tumors compared with adjacent non-cancerous tissues. The level of BAF250a protein expression was higher in 10 of 12 HCC tumors compared with adjacent liver tissues. IHC indicated that 12.17 % of HCC tumors (14/115) were BAF250a-negative. Loss of BAF250a was significantly associated with larger tumor size, but not associated with other clinicopathologic features. There was no significant difference in disease-free or overall survival between BAF250a-positive and BAF250a-negative patients. Most HCCs had an increased level of *ARID1A* mRNA and BAF250a expression. Loss of BAF250a was significantly more frequent in larger HCC tumors, but had no prognostic significance.

Keywords Hepatocellular carcinoma · ARID1A · BAF250a · Tumor suppressor gene

Introduction

Liver cancer is one of the most prevalent cancers worldwide, comprised of diverse, histologically-distinct hepatic neoplasms. Hepatocellular carcinoma (HCC) is among the most lethal liver cancers, representing 70 %–90 % of primary liver cancers [1, 2].

Various HCC-relevant genes and pathways have been elucidated, such as the tumor suppressor *p53*, *β-catenin*, and components of PI3K/Ras signaling. Recent exome sequencing studies have revealed that the AT-rich interactive domain 1A (*ARID1A*), a factor in the chromatin remodeling complex, is frequently mutated in patients with HCC [3–5].

There are two major classes of chromatin remodeling complexes (ATP-dependent remodeling complexes and HAT or HDAC complexes) [6]. The switching defective/sucrose non-fermenting (SWI/SNF) family remodelers are part of the ATP-dependent nucleosome remodeling system and can be further divided into BAF and PBAF according to different catalytic subunits. *ARID1A* encodes the BAF250a protein, which is a subunit of BAF [7].

Increasing data have implicated ARID1A as a tumor suppressor. Frequent *ARID1A* mutations were first described in various gynecologic tumors, including ovarian clear cell carcinoma [8], endometriosis-associated ovarian carcinomas [9], and endometrial carcinomas [10]. Corollary studies have shown that *ARID1A* is also mutated in other cancer subtypes, such as HCC, renal cell carcinoma [11], gastric cancer [12], cholangiocarcinoma [13], colon and rectal cancer [14], and lung cancer [15].

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Some functional studies have elucidated the mechanisms of tumor suppression by ARID1A. Wild-type ARID1A expression is sufficient to suppress cell proliferation in ovarian cancer cells with endogenous mutant *ARID1A*. Knockdown of ARID1A enhances proliferation of normal ovarian surface epithelial cells [16]. In gastric cancer cells, depletion of ARID1A by small interfering RNA (siRNA) enforces migration and invasion, whereas ectopic expression of ARID1A inhibits migration [17]. ARID1A has been shown to be a regulator of the response to FAS activation in Jurkat leukemia cells [18]. Another study reported that loss of BAF250a results in decatenation defects and G2/M delay in mouse embryonic fibroblasts [19]. Moreover, inactivation of the SWI/SNF complexes results in decreased DSB repair, which contributes to the role as a tumor suppressor [20].

Although *ARID1A* has recently been implicated as a major tumor suppressor gene, the clinicopathologic significance in HCC is not clear. In the current study we determined the expression of ARID1A (BAF250a) in two series of HCC patients using quantitative real-time PCR (qPCR) and immunohistochemistry (IHC). Interestingly, we showed that up-regulation of ARID1A occurs frequently in HCC tumors compared with adjacent non-cancerous tissues. Loss of BAF250a was shown to be related to tumor size, but had no prognostic significance in patients with HCC.

Materials and Methods

Patient Information

Two series of HCC patients were used in the current study. One series included 12 consecutive paired HCC tumors and adjacent non-cancerous tissues from the same patient. The patients underwent laparoscopic liver resection between January and June 2014 in our institution. Messenger RNA expression of *ARID1A* in fresh frozen tissues was tested by qPCR and BAF250a expression was evaluated by IHC. The other series included 121 consecutive HCC patients who underwent liver resection in our Surgery Department between 2008 and 2011. HCCs from patients tested by IHC for BAF250a. The clinical information was retrieved from the hospital information system retrospectively. All HCC patients were clinically-staged according to the BCLC staging system [21].

All patients were followed regularly. The minimum follow-up time was 36 months; 14 patients were lost to follow-up. The median follow-up time was 38 months (range, 3–72 months). Written informed consent was obtained from each enrolled patient and the study protocol was approved by the Ethics Committee of Sir Run Run Shaw Hospital. The data were analyzed anonymously.

Quantitative Real-Time PCR (qPCR)

Total RNA was extracted using Trizol reagent (Ambion, Carlsbad, CA, USA) and reverse transcribed to cDNA using PrimeScript™ RT Master Mix (TaKaRa, Shiga, Japan). The qPCR was performed on a 7500 RT-PCR System (Applied Biosystems, Warrington, UK) using the POWER SYBR Green PCR Master Mix detection system (Applied Biosystems). The cycling parameters were as follows: 1 cycle at 50 °C for 2 min; 1 cycle at 95 °C for 10 min; and 40 cycles at 95 °C for 15 s, 60 °C for 31 s, and 72 °C for 31 s. GAPDH was chosen as an internal control for the normalization of the total cDNA. The primers used were as follows: GAPDH forward, 5′-CGACCACTTTGTCAAGCTCA-3′; GAPDH reverse, 5′-TTACTCCTTGGAGGCCATGT-3′; ARID1A forward, 5′-GGCGGGACTAACCCATACTC-3′; and ARID1A reverse, 5′-GGCCCTGTTGACCATACCC-3′. Experiments were performed in triplicate.

IHC

HCC specimens were fixed in formalin, embedded in paraffin, and sectioned at a thickness of 4 mm in the Department of Pathology of Sir Run Run Shaw Hospital. Paraffin sections were dewaxed in xylene and ethanol. Epitope retrieval was performed in 10 mM citrate buffer (pH 6.0) at 95 °C for 20 min in a microwave oven. Endogenous peroxidase activity was blocked by 0.3 % H_2O_2 in PBS for 10 min. Tissue antigens were unmasked and the sections were incubated overnight with anti-ARID1A antibody (diluted 1:1000; ab182560; Abcam, Cambridge, MA, USA). The sections were incubated with diluted biotinylated goat anti-rabbit IgG antibody (Vector Laboratories, Burlingame, CA, USA) for 30 min at room temperature. Chromogenic reactions were carried out according to the protocols of the ImmPACT™ DAB Kit (Vector Laboratories).

BAF250a is a nuclear localization protein. Tumor cells were classified as positive if tumor cells showed definite nuclear staining, and negative if tumor nuclei had no immunoreactivity and non-tumor cells in the same sample showed immunoreactivity. Cases in which neither non-tumor cells nor tumor cells were immunoreactive were considered as technical failures and were excluded. A semi-quantitative method was used for staining assessment. Nuclear staining intensity was scored as follows: 0 = negative; 1 = low; 2 = moderate; and 3 = high. Staining frequency was scored as 0 (<5 % positive tumor cells), 1 (5 %–25 % positive tumor cells), 2 (25 %–50 % positive tumor cells), and 3 (>50 % positive tumor cells). Relative quantification (RQ) units were calculated as the product of the average staining intensity and frequency. RQ units =0 or 1 indicated negative cases, whereas RQ units ≥2 were regarded as positive cases. All slices were observed and RQ units were calculated independently by three observers.

Statistical Analysis

Measurement data from qPCR were expressed as the mean ± standard deviation. RQ units from IHC were shown as the median and range. Cases were categorized into subgroups based on the staining results for BAF250a. The Wilcoxon signed rank test and Fisher exact test were used. The data were censored when patients were lost to follow-up. Disease-free and overall survival data were determined using the Kaplan–Meier method and compared using the log-rank test. Statistical significance was defined as a $P < 0.05$.

Results

ARID1A mRNA and Protein Expression in HCC Tumors and Non-Cancerous Liver Tissues

We first tested the level of *ARID1A* mRNA in 12 paired HCC tumors and adjacent non-cancerous tissues using qPCR. The mean level of *ARID1A* mRNA in HCC tumors (0.051 ± 0.025 [normalized by GAPDH]) was significantly higher than non-cancerous tissues (0.020 ± 0.012 [normalized by GAPDH]; Supplemental Table S1). Increased *ARID1A* mRNA levels were noted in HCC tumors compared with non-cancerous tissues in ten of 12 patients (83.33 %; $P = 0.002$, Wilcoxon signed rank test; Fig. 1 and Table 1).

To validate the up-regulation of ARID1A expression in HCC tumors, we determined the level of BAF250a protein by IHC. The expression of BAF250a was higher in HCC tumors (median, 9) compared with adjacent non-cancerous tissues (median, 3.5; Supplemental Table S1). In 83.33 % (10/12) of the cases, BAF250a expression was significantly higher ($P = 0.006$, Wilcoxon signed rank test; Fig. 2 and Table 1).

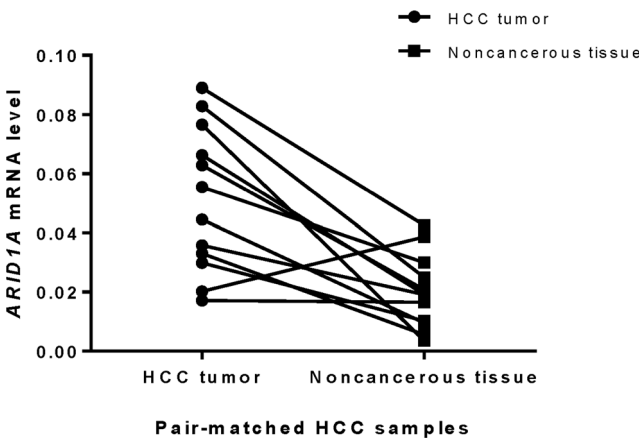

Fig. 1 ARID1A mRNA levels are higher in most HCC tumors compared with adjacent non-cancerous tissues, as assessed by qPCR. The values were normalized by GAPDH. *Dots* represent the level of ARID1A mRNA in the HCC tumors and the *squares* represent the level of ARID1A mRNA in the non-cancerous liver tissues

Table 1 ARID1A/BAF250a Expression in pair-matched HCC samples

Variable	Cases	*P* Value
ARID1A mRNA level		
Higher in tumor vs paratumor tissue	10 (83.33 %)	0.002
Lower in tumor vs paratumor tissue	0	
No significant difference	2 (16.67 %)	
BAF250a protein RQ units		
Higher in tumor vs paratumor tissue	10 (83.33 %)	0.006
Lower in tumor vs paratumor tissue	1 (8.33 %)	
No significant difference	1 (8.33 %)	

P value was calculated using the Wilcoxon signed rank test

Association Between BAF250a Status and Clinicopathologic Factors in Patients with HCC

To further illustrate the association between BAF250a status and clinicopathologic factors, we tested 121 HCC tumors for BAF250a by IHC. Six cases were excluded because of staining failure. One hundred fifteen cases were enrolled and classified as negative or positive (see Materials and Methods). Representative staining from negative and positive HCC tumors is shown in Fig. 3; there were 14/115 (12.17 %) negative cases.

We analyzed the possible correlation between BAF250a status and clinical characteristics, and the results are shown in Table 2. BAF250a expression was significantly correlated with tumor size. A higher proportion of large tumors (8/28 [28.57 %]) were BAF250a negative compared with small tumors (6/87 [6.90 %]; $P = 0.005$); however, the BAF250a status was not significantly associated with patient gender, age, cirrhosis, HBV status, fatty liver status, tumor number, portal vein invasion, AFP level, and BCLC stage.

Prognostic Significance of BAF250a in HCC

To determine whether or not BAF250a can be used as a prognostic marker, we compared the disease-free and overall survival among patients with positive and negative expression of BAF250a using the Kaplan–Meier method and log-rank test (Fig. 4). The median disease-free survival of BAF250a-positive patients was 62 months, which was longer than BAF250a-negative patients (48 months), although there was no statistically significant difference ($P = 0.570$ [log-rank test]). There was also no significant difference in overall survival ($P = 0.612$ [log-rank test]) between the BAF250a-positive (63 months) and BAF250a-negative patients (60 months).

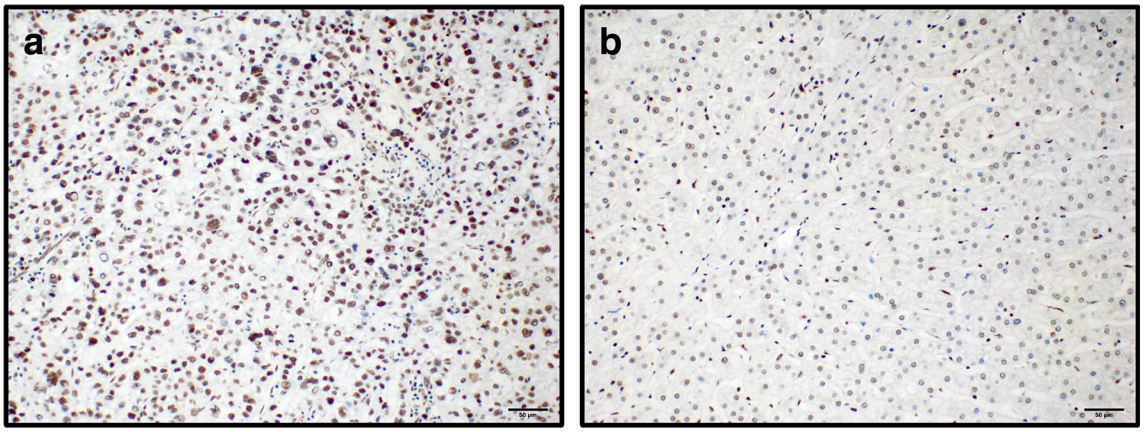

Fig. 2 BAF250a is up-regulated in most HCC tumors compared with adjacent non-cancerous tissues, as assessed by IHC. Representative specimens from HCC tumor (**a**) and non-cancerous liver tissues from the same patient (**b**). Original magnification, ×200

Discussion

HCC is a malignant cancer with abundant heterogeneity. Hepatocarcinogenesis is considered to be a multi-step process of oncogenic activation and tumor suppressor inactivation [22]. Genome sequencing has elucidated a number of genetic alterations in HCCs; however, our understanding regarding the genetic alterations underlying the occurrence and development of HCC is still limited. Thus, a better understanding of the molecular genetic evidence in HCC may facilitate better prognostication and treatment by stratifying patients.

*ARID1*A is one of the most commonly mutated genes in HCC [3–5], and is considered to be an important suppressor gene; however, the relationship between ARID1A status and clinicopathologic characteristics is not clear. Our study provides the examination of this issue.

In this study, we showed that the level of *ARID1A* mRNA is higher in most HCC samples compared with pericarcinomatous tissues, which was also confirmed by IHC. Our results were in contrast to studies involving other cancers. One study about breast cancer showed that the expression of *ARID1A* mRNA was lower in cancer than corresponding normal tissues [23]. Cho et al. [24] reported that BAF250a expression gradually decreased during the transition from normal cervical tissue to cervical carcinoma. Zhang et al. [25] reported that the expression of BAF250a was down-regulated in endometrial carcinoma compared with normal endometrial tissues. The discrepant results could be attributed to tissue and organ specificity, and our preliminary study suggested there may be a potential novel function of ARID1A in liver cancer.

Moreover, we showed that BAF250a IHC staining was negative in 12.17 % of the HCC patients. The status of BAF250a was significantly associated with tumor size. The same findings have also been demonstrated in gastric cancer [26], breast cancer [23], cervical cancer [24], and colorectal carcinoma [27]. According to Guichard et al. [4], *ARID1A* mutations are significantly more frequent in HCC related to alcohol intake. In our series, there was no relationship

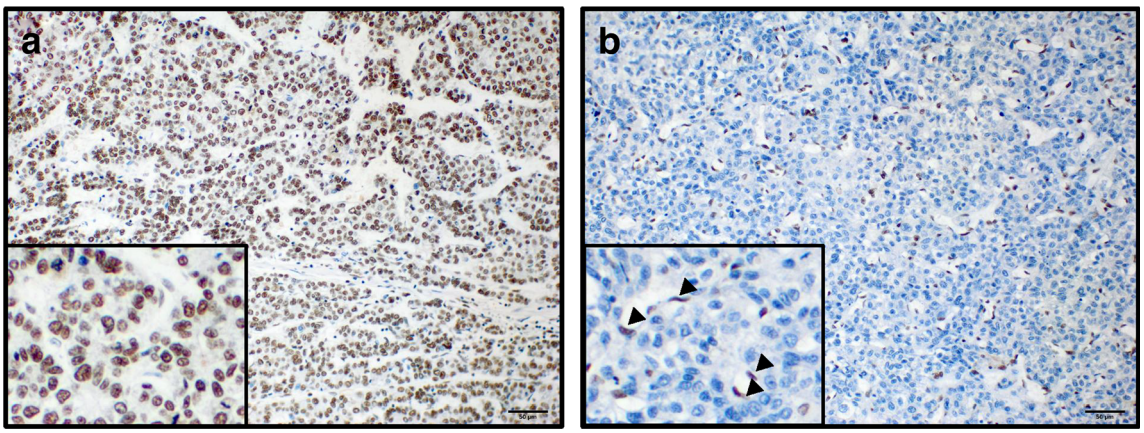

Fig. 3 Representative immunohistochemical staining of BAF250a in HCC tumors. Positive case (**a**) and negative case (**b**). Original magnification, ×200. *Arrowheads* indicate the inflammatory and stromal cells that are positive for BAF250a in the negative case (**b**). The insets are high-magnification views (×400)

Table 2 Relationship between BAF250a expression and the clinicopathologic features of HCC

Variable	Total Patients (n)	BAF250a-Positive (n)	BAF250a-Negative (n)	*P* Value[a]
Gender				
Male	94	81	13	0.460
Female	21	20	1	
Age (years)				
>60	34	29	5	0.755
≤60	81	72	9	
Cirrhosis				
Yes	74	66	8	0.563
No	41	35	6	
HBV infection				
Yes	97	87	10	0.230
No	18	14	4	
Fatty liver				
Yes	4	4	0	1.000
No	111	97	14	
Tumor size				
>5 cm	28	20	8	0.005
≤5 cm	87	81	6	
Tumor number				
>3	1	1	0	1.000
≤3	114	100	14	
Portal vein tumor thrombus				
Yes	1	0	1	0.122
No	114	101	13	
AFP level				
>25 ng/ml	59	51	8	0.778
≤25 ng/ml	56	50	6	
BCLC stage				
0 + A	113	100	13	0.230[b]
B + C	2	1	1	

[a] Fisher's exact test

[b] Columns were combined before calculation

between BAF250a level and other clinicopathologic variables, including fatty liver status, cirrhosis, and HBV status. This discrepancy may be due to differences in the etiology of HCC.

The significance of BAF250a for prognostic evaluation is controversial. For instance, in patients with ovarian clear cell carcinoma, loss of ARID1A expression is related to a shorter progression-free survival and chemoresistance [28]. In patients with endometrial carcinoma or clear cell carcinoma of the endometrium, however, there is no significant correlation between the level of ARID1A expression and survival [29, 30]. We did not conclude that BAF250a status has prognostic significance. However, considering the potential correlation between tumor size and prognosis [31], a larger series of patients is needed to confirm the prognostic significance of ARID1A expression in HCC.

Recent studies have revealed that *ARID1A* is frequently mutated in a variety of cancers, but the exact mechanism is not understood. According to our results, there are two possible explanations for the loss of BAF250a in HCC. First, the change in ARID1A expression is an early event in the development of HCC. Mutations or silencing of BAF250a will accelerate cellular proliferation; however, this hypothesis cannot explain the up-regulation of ARID1A in the majority of HCC tumors compared with adjacent liver tissues. The other possibility is that the level of ARID1A is low in normal tissues, but with the emergence of cancer, ARID1A is increased to prevent unlimited cellular proliferation. The higher frequency of ARID1A-negative cases in larger tumors suggests that alterations in this gene may occur in late stages of HCC progression. Tumors can escape the inhibition via *ARID1A* gene mutations. These two hypotheses can be verified by determining the level of ARID1A expression in the same patient at different stages. But it would be difficult to obtain those samples. In addition, other important genes including *p53*, *β-catenin* should also been considered in the development

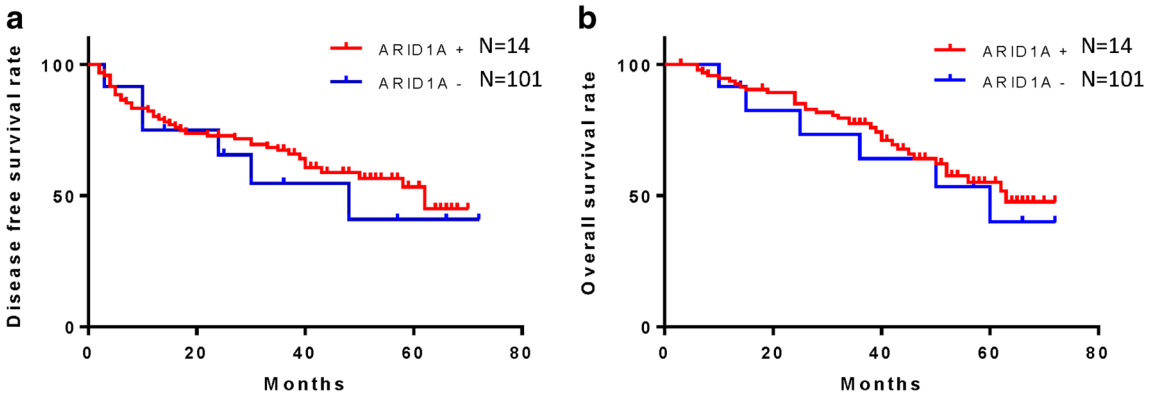

Fig. 4 Kaplan–Meier survival analysis of patients with positive and negative expression of BAF250a. No significant difference existed in the disease-free (**a**) ($P = 0.570$, log-rank test) and overall survival rates (**b**) ($P = 0.612$, log-rank test) between the BAF250a-positive and BAF250a-negative sub-groups

of HCC. BAF250a may be one of the genes that are involved in the regulation of proliferation, but not the only one.

It must be noted that our research had some limitations. First, qPCR or IHC analyses cannot be completely equated with the detection of mutations. We cannot rule out missense mutations in BAF250a-positive cases. Similarly, the expression of ARID1A can be inactivated by epigenetic mechanisms. Second, the patients enrolled in our study were surgical patients, which resulted in selection bias. In our series, only two patients were BCLC stage B or C, and the number of ARID1A-negative patients was small. These factors can impact the power of statistical analysis. In addition, we ignored the post-operative adjuvant treatment in our patients, such as transarterial chemoembolization, which may have affected the oncologic outcome. Therefore, further studies with a larger number of patients are warranted to confirm the clinicopathologic significance of *ARID1A* mutations and loss of expression in HCC.

In conclusion, we have reported the status of BAF250a (ARID1A) expression in HCC. Increased levels of *ARID1A* mRNA and BAF250a protein were noted in the majority of HCC tumors compared with adjacent noncancerous tissues. Of the HCC tumors, 12.17 % were BAF250a-negative based on IHC analysis. In addition, we examined the relationship between clinicopathologic features and the level of ARID1A expression. Loss of BAF250a expression was significantly correlated with larger tumor size, but did not correlate with other features. There were also no significant differences between ARID1A-positive and ARID1A-negative cases with respect to prognostic value. Further studies are needed to identify the function of ARID1A in the occurrence and progression of HCC.

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Compliance with Ethical Standards

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Conflict of Interest All authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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