

## UNIVERSAL HEPATITIS B VACCINATION IN TAIWAN AND THE INCIDENCE OF HEPATOCELLULAR CARCINOMA IN CHILDREN

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**ABSTRACT**

**Background** A nationwide hepatitis B vaccination program was implemented in Taiwan in July 1984. To assess the effect of the program on the development of hepatocellular carcinoma, we studied the incidence of this cancer in children in Taiwan from 1981 to 1994.

**Methods** We collected data on liver cancer in children from Taiwan's National Cancer Registry, which receives reports from each of the country's 142 hospitals with more than 50 beds. Data on childhood liver cancer were also obtained from Taiwan's 17 major medical centers. To prevent the inclusion of cases of hepatoblastoma, the primary analysis was confined to liver cancers in children six years of age or older. Data were also obtained on mortality from liver cancer among children.

**Results** The average annual incidence of hepatocellular carcinoma in children 6 to 14 years of age declined from 0.70 per 100,000 children between 1981 and 1986 to 0.57 between 1986 and 1990, and to 0.36 between 1990 and 1994 ( $P < 0.01$ ). The corresponding rates of mortality from hepatocellular carcinoma also decreased. The incidence of hepatocellular carcinoma in children 6 to 9 years of age declined from 0.52 for those born between 1974 and 1984 to 0.13 for those born between 1984 and 1986 ( $P < 0.001$ ).

**Conclusions** Since the institution of Taiwan's program of universal hepatitis B vaccination, the incidence of hepatocellular carcinoma in children has declined. (N Engl J Med 1997;336:1855-9.)

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**H**EPATOCELLULAR carcinoma is closely associated with hepatitis virus infections, particularly infection with hepatitis B virus (HBV).<sup>1-6</sup> However, the cause-and-effect relation of HBV to hepatocellular carcinoma is as yet unproved. In Taiwan the association between hepatocellular carcinoma and HBV is stronger in children than in adults. The rate of seropositivity for hepatitis B surface antigen (HBsAg) approaches 100 percent in children with hepatocellular carcinoma,<sup>7,8</sup> as compared with 70 to 80 percent in adults with the disease. Integration of the HBV genome into the host genome of hepatocellular carcinoma has been reported in children.<sup>9</sup>

To control hepatitis B, Taiwan launched a nationwide vaccination program in 1984.<sup>10,11</sup> In 10 years, this program reduced the HBsAg carrier rate in children from 10 percent to less than 1 percent.<sup>12</sup> How-

ever, it remains unclear whether the ultimate goal of reducing HBV-induced mortality, particularly that from hepatocellular carcinoma, can be achieved. Since the incidence of hepatocellular carcinoma in Taiwan peaks in the sixth decade of life,<sup>6</sup> it may take 40 years or longer to see an overall decrease in the rate of hepatocellular carcinoma as a result of the vaccination program. The rate of hepatocellular carcinoma in children can be considered as an early indicator of the effectiveness of vaccination in reducing the rate of hepatocellular carcinoma. A decrease in the rate in children after universal vaccination against hepatitis B would provide further evidence that HBV is a cause of hepatocellular carcinoma.

**METHODS****Population Data**

In Taiwan, which has a population of 21 million, the health care system changed little from 1981 to 1994. All births, deaths, marriages, and divorces must be registered with the government's household-registration offices. Information on education, employment, and migration is also recorded. These records are double-checked annually by registration officers, who conduct home visits. Demographic data obtained from household-registration offices are complete and accurate. The year-end population statistics for children used in this study were obtained from the annual reports on demographic statistics published by the Ministry of Interior.

**Nationwide Hepatitis B Vaccination Program**

Taiwan's mass-vaccination program against hepatitis B was launched in July 1984.<sup>10,11</sup> For the first two years, the program covered only neonates born to mothers who were HBsAg carriers, but it was extended to all neonates in July 1986, to preschool children in July 1987, to primary-school children in 1988, to middle-school children in 1989, and to adults in 1990. Infants were given 5- $\mu$ g doses of a plasma-derived HBV vaccine (Hevac B, Institut Pasteur, Marnes-la-Coquette, France) at birth and at 1, 2, and 12 months of age. In addition, 0.5 ml (145 IU) of hepatitis B immune globulin (Abbott Laboratories, Cutter, or Green Cross, Taiwan) was given within 24 hours after birth to infants whose mothers had hepatitis B e antigen (HBeAg) or reciprocal serum titers of HBsAg higher than 2560. Since November 1992, recom-

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binant HBV vaccines have replaced plasma-derived vaccines and have been given at birth and at one and six months of age. The government has covered all the costs of the program. Those who miss the scheduled vaccination are encouraged to receive hepatitis B vaccines on a fee-for-service basis. In addition, HBV vaccine paid for by parents was given to preschool children from 1987 to 1994. The estimated vaccine coverage from 1981 to 1994 in infancy and at six years of age is shown in Table 1.

**Inclusion Criteria for Cases of Childhood Hepatocellular Carcinoma**

All cases of liver cancer among children 6 to 14 years of age in Taiwan between 1981 and 1994 were included in our study except those that were a type other than hepatocellular carcinoma. Children younger than six years old were also excluded to prevent the inclusion of cases of hepatoblastoma.<sup>13,14</sup>

**Trends in the Annual Incidence of Childhood Hepatocellular Carcinoma**

To look for trends in the incidence of childhood hepatocellular carcinoma after the program was implemented, we used three systems to study the incidence of this disease from July 1981 to June 1994. July 1 was used as a starting point for each year because the vaccination program was launched on July 1, 1984.

**System 1: National Cancer Registry**

We analyzed information, obtained from the data bank of the Taiwan National Cancer Registry of the Department of Health, on cases that occurred between July 1981 and June 1994 in children under 14 years of age. This registry was established in 1979. Cases of cancer at each of Taiwan's 142 hospitals with more than 50 beds were reported. We used data from 1981 onward to avoid possible gaps in reporting of data at the beginning of this system. The items registered included the patient's name, national identification number, date of birth, sex, date of diagnosis, location of tumor, and histologic data.

**System 2: Multicenter Childhood Hepatocellular Carcinoma Registration Study**

To ensure the accuracy of the data from the National Cancer Registry, we simultaneously conducted a multicenter collaborative study of the registry of childhood hepatocellular carcinoma. Pediatric gastroenterologists or oncologists from 17 major hospitals, including all 10 tertiary referral centers in Taiwan, participated in this study. In addition to the data in the National Cancer Registry, this study included information on serum concentrations of HBsAg, alpha-fetoprotein levels, and history of vaccination against hepatitis B.

The data collected from these two systems were then merged, and the cases that did not overlap were added together after each was confirmed by the reporting hospital. According to the capture-recapture method,<sup>15</sup> the total number of children with hepatocellular carcinoma during the study period is estimated to be 294 (95 percent confidence interval, 272 to 316). The cases identified by systems 1 and 2 are estimated to be 84 percent of all cases of childhood hepatocellular carcinoma. The rate was not affected by age.

**System 3: National Mortality Registry**

Data on deaths in Taiwan between 1969 and 1993 among children under 15 years of age were also analyzed for trends in mortality resulting from childhood hepatocellular carcinoma during the study period.

Death certificates, which must be registered with the household-registration offices, are routinely reviewed and submitted to the national death-certification system by local health centers. By law, a certificate must be registered within one month of a death. All certificates are reviewed and coded by medical registrars according to the *Manual of the International Statistical Classifica-*

**TABLE 1. ESTIMATED HEPATITIS B VACCINE AND HEPATITIS B IMMUNE GLOBULIN (HBIG) COVERAGE RATES IN INFANTS AND HEPATITIS B VACCINE COVERAGE RATE AND HBsAg SEROPREVALENCE IN SIX-YEAR-OLDS.\***

YEAR (JULY TO JUNE)	INFANTS		SIX-YEAR-OLDS	
	VACCINE	HBIG	VACCINE	HBsAg POSITIVITY
	percent			
1981-1982	0	0	0	9.7
1982-1983	0	0	0	10.6
1983-1984	0	0	0	10.6
1984-1985	15†	4.8	0	9.8
1985-1986	15†	5.9	0	9.8
1986-1987	86	5.2	12‡	4.7
1987-1988	90	5.4	12‡	4.7
1988-1989	86	5.4	14‡	3.9
1989-1990	94	5.3	14‡	3.9
1990-1991	92	4.4	23‡‡	0.9
1991-1992	84	3.9	23‡‡	0.9
1992-1993	85	5.0	90	0.8
1993-1994	84	4.8	96	0.8

\*The hepatitis B vaccine coverage rate and HBsAg seroprevalence in infancy and at the age of six were estimated on the basis of data from previous field studies.<sup>12</sup>

†The immunization was given only to infants born between 1984 and 1986 to high-risk mothers.

‡The coverage from 1986 to 1992 was partially attributable to vaccination in the preschool period.

*tion of Diseases, Injuries, and Causes of Death*<sup>16</sup> in the central office of the national death-certification system. The diagnosis and classification of underlying causes of death in Taiwan vary from area to area according to the level of medical services. In some cases, primary liver cancer may not be listed as the underlying cause for children who in fact died from the disease, since other diagnostic terms may sometimes be used to describe the immediate cause of death. On the other hand, some metastatic liver tumors may be misclassified as primary liver cancer. Therefore, the mortality data were not merged with the more reliable incidence data.

**Incidence of Brain Tumors as a Control Variable**

The incidence of brain tumors, common malignant tumors in children 6 to 14 years of age, was used as a control variable. The diagnosis is usually not difficult, and there was no reason to expect any change in incidence during the study period.

**Correlation between History of HBV Vaccination and Childhood Hepatocellular Carcinoma**

The history of vaccination against hepatitis B, including the date of administration of each dose of hepatitis B vaccine and hepatitis B immune globulin, has been registered at the national level for each neonate in the program since July 1984, the beginning of the nationwide vaccination program.<sup>10</sup> This record was retrieved and reviewed for each child with hepatocellular carcinoma born after July 1984.

**Statistical Analysis**

The annual incidence of childhood hepatocellular carcinoma was determined by dividing the annual number of cases in children 6 to 14 years of age by the year-end population of children

of the same age. The statistical significance of the difference in the incidence of childhood hepatocellular carcinoma for the two periods under comparison was examined by using the Poisson test.<sup>17</sup>

In order to compare the incidence rates in annual cohorts born between July 1975 and June 1988, the incidence among children in a given birth cohort was calculated by dividing the number of cases of hepatocellular carcinoma by the total number of person-years observed when the subjects were 6 to 14 years old. The effect of the nationwide vaccination program on the incidence of hepatocellular carcinoma was assessed by Poisson regression analysis, with control for year of birth (before or after July 1984), age, and vaccination status.

## RESULTS

The average incidence of hepatocellular carcinoma in children 6 to 14 years of age from 1981 to 1986 was 0.70 per 100,000 children (range, 0.65 to 0.78). The average incidence declined to 0.57 (range, 0.48 to 0.62) for the period from 1986 to 1990 and to 0.36 for the period from 1990 to 1994 (range, 0.23 to 0.48). The ratio of the average incidence in the period from 1986 to 1990 to that in the period from 1982 to 1986 was 0.81. This decline may have been due to the herd immunity that resulted from the mass-vaccination program and the vaccination of preschool-age children. The ratio of the incidence in the 1990-to-1994 period to that in the 1986-to-1990 period was 0.63. This faster decline was attributed to the direct effect of mass vaccination. The incidence from 1990 to 1994 was significantly lower than that from 1981 to 1990 ( $P < 0.01$ ) (Table 2). The age-adjusted relative risk of hepatocellular carcinoma after as compared with before July 1990 was 0.33 ( $P < 0.001$ ).

The mortality rate in children with hepatocellular carcinoma showed a parallel decline (Table 2). The age-adjusted relative risk of death after as compared with before July 1990 was 0.51 ( $P < 0.001$ ).

In contrast, the incidence of brain tumors in children 6 to 14 years old did not show a similar decrease during the period of observation, according to the same registration system (Table 2). The overall incidence of childhood cancer also did not show such a decrease during this period (data not shown). By contrast, the incidence of liver cancer in people over 14 years of age increased from 11.11 to 25.82 per 100,000 population from 1981 to 1992 (Table 3). The incidence of liver cancer in children up to five years of age changed little during the same period (Table 3). The age-adjusted relative risk of liver cancer in children up to five years of age after as compared with before July 1984 was 0.97 ( $P = 0.91$ ).

An analysis of the incidence of liver cancer according to year of birth showed that the incidence among children 6 to 14 years old declined from 0.64 per 100,000 person-years for the cohort born between July 1975 and June 1976 to 0.1 per 100,000 person-years for the cohort born between July 1985 and June 1986 (Fig. 1). However, the incidence among children up to five years of age did not de-

**TABLE 2. ANNUAL INCIDENCE OF HEPATOCELLULAR CARCINOMA (HCC) AND BRAIN TUMOR IN CHILDREN 6 TO 14 YEARS OF AGE.**

YEAR (JULY TO JUNE)	POPULATION	INCIDENCE OF HCC*			INCIDENCE OF BRAIN TUMOR
		INCIDENCE OF HCC*	MORTALITY FROM HCC	number (rate per 100,000)	
1981-1982	3,324,398	26 (0.78)	35 (1.05)	28 (0.84)	
1982-1983	3,375,164	24 (0.71)	20 (0.59)	30 (0.89)	
1983-1984	3,380,070	22 (0.65)	31 (0.92)	40 (1.18)	
1984-1985	3,398,595	22 (0.65)	22 (0.65)	40 (1.18)	
1985-1986	3,429,370	25 (0.73)	27 (0.79)	38 (1.11)	
1986-1987	3,458,348	20 (0.58)	18 (0.52)	38 (1.10)	
1987-1988	3,506,520	17 (0.48)	24 (0.68)	38 (1.08)	
1988-1989	3,545,417	21 (0.59)	22 (0.62)	56 (1.58)	
1989-1990	3,558,849	22 (0.62)	18 (0.51)	56 (1.57)	
1990-1991	3,556,671	15 (0.42)	18 (0.51)	45 (1.27)	
1991-1992	3,481,648	10 (0.29)	8 (0.23)	55 (1.58)	
1992-1993	3,404,962	8 (0.23)	11 (0.32)	52 (1.53)	
1993-1994	3,320,455	16 (0.48)	10 (0.30)†	44 (1.33)†	

\* $P < 0.01$  for the comparison of values before July 1990 with those after July 1990.

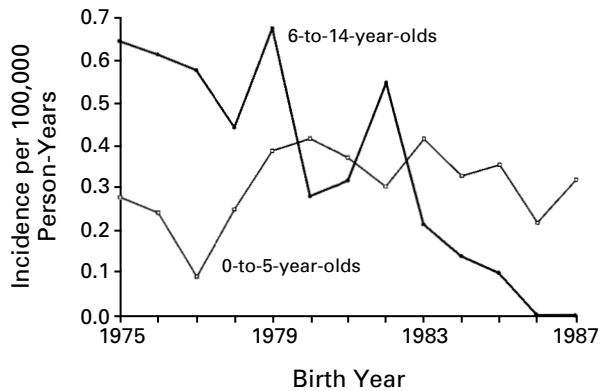
†These values are based on data for July to December 1993.

**TABLE 3. ANNUAL INCIDENCE OF LIVER CANCER PER 100,000 PEOPLE OVER 14 OR UNDER 6 YEARS OF AGE.**

YEAR (JULY TO JUNE)	>14 YEARS OLD		0-5 YEARS OLD	
	POPULATION	NO. OF CANCERS (INCIDENCE)	POPULATION	NO. OF CANCERS (INCIDENCE)
1981-1982	12,403,835	1378 (11.11)	2,406,801	13 (0.54)
1982-1983	12,692,867	1414 (11.14)	2,387,704	8 (0.34)
1983-1984	12,964,397	1610 (12.42)	2,387,902	12 (0.50)
1984-1985	13,274,772	1889 (14.23)	2,338,577	8 (0.34)
1985-1986	13,562,074	2135 (15.74)	2,266,672	4 (0.18)
1986-1987	13,814,950	2630 (19.04)	2,181,312	2 (0.09)
1987-1988	14,090,025	2969 (21.07)	2,076,067	11 (0.53)
1988-1989	14,342,061	3238 (22.58)	2,016,270	8 (0.40)
1989-1990	14,581,175	3322 (22.78)	1,967,962	7 (0.36)
1990-1991	14,843,329	3482 (23.46)	1,952,966	6 (0.31)
1991-1992	15,144,918	3910 (25.82)	1,930,276	4 (0.21)
1992-1993	15,405,527	3760 (24.41)	1,941,658	9 (0.46)
1993-1994	7,849,470	1773 (22.59)*	1,959,250	10 (0.51)

\*This value is based on data for July to December 1993.

cline for the cohorts born from 1974 to 1986 (Fig. 1). There was a slow decline in the incidence of hepatocellular carcinoma among children 6 to 14 years old who were born before the start of the vaccination program (between 1980 and 1984) and a faster decline among those born after the start of the program (between 1984 and 1988) (Fig. 1). The Poisson regression analysis showed that the relative risk of liver cancer was 0.34 in children 6 to 14 years old



**Figure 1.** Comparison of the Incidence of Liver Cancer in Children 6 to 14 and 0 to 5 Years of Age, According to Birth Cohort.

The incidence of liver cancer in children 6 to 14 years old declined, whereas the incidence in children 0 to 5 years old remained essentially unchanged. This may be explained by the reduction in the rates of both horizontal and perinatal transmission of HBV infection that resulted from the mass-vaccination program, which benefited the younger cohorts directly and the elder cohort indirectly by decreasing the reservoir of infection and reducing the risk of horizontal infection. The incidence of liver cancer in children between 6 and 14 years old declined to zero for children born in 1986 and 1987. The observed number of person-years for those born in 1986 was 613,837, and for those born in 1987 it was 313,311.

**TABLE 4.** INCIDENCE OF LIVER CANCER PER 100,000 CHILDREN IN BIRTH COHORTS DETERMINED ACCORDING TO THE DATE OF IMPLEMENTATION OF THE HEPATITIS B VACCINATION PROGRAM.

AGE AT DIAGNOSIS (YR)	BEFORE-PROGRAM COHORT (JULY 1974–JUNE 1984)		AFTER-PROGRAM COHORT (JULY 1984–JUNE 1986)	
	POPULATION	NO. OF CANCERS (INCIDENCE)	POPULATION	NO. OF CANCERS (INCIDENCE)
6	3,940,747	18 (0.46)	648,642	0 (0.00)
7	3,938,119	21 (0.53)	647,051	1 (0.15)
8	3,931,983	19 (0.48)	644,892	2 (0.31)
9	3,928,721	24 (0.61)	340,521*	0 (0.00)
Total	15,739,570	82 (0.52)	2,281,106	3 (0.13)†

\*This value is based on data for the cohort born from July 1984 to June 1985.

† $P < 0.001$  for the comparisons between birth cohorts.

born after the implementation of the vaccination program, as compared with those born before the program, after adjustment for age and year of birth ( $P = 0.03$ ). From 1974 to 1984, hepatocellular carcinoma was diagnosed in a total of 82 children among Taiwan's approximately 15.7 million children who were between the ages of six and nine years at any time during this period (0.52 per 100,000). From 1984 to 1986, hepatocellular carcinoma was diagnosed in only three children between the ages of six and nine among a population of about 2.3 million (0.13 per 100,000) ( $P < 0.001$ ) (Table 4).

These three children, all boys born in 1985, received four doses each of hepatitis B vaccine. Two were born to HBsAg-carrier mothers and received hepatitis B immune globulin at birth. Both tested seropositive for HBsAg and hepatitis B e antibody when hepatocellular carcinoma was diagnosed. The third child and his mother consistently tested seronegative for HBsAg. Hepatocellular carcinoma was confirmed in the child by histologic examination. Polymerase-chain-reaction assays detected HBV genome in both the tumorous and nontumorous liver tissue of this child. All three children had markedly elevated serum alpha-fetoprotein levels and space-occupying lesions in the liver. All three died.

## DISCUSSION

This study in Taiwan shows that 6 to 10 years after the initiation of the hepatitis B mass-vaccination program, the incidence of childhood hepatocellular carcinoma declined significantly. These data are evidence that prevention of a viral infection in a population can reduce the incidence of a specific cancer.

Three lines of evidence support our finding of a decline in the rate of childhood hepatocellular carcinoma after the initiation of the Taiwanese hepatitis B vaccination program. First, data from three different registration systems consistently showed similar trends toward decreases in childhood hepatocellular carcinoma during the observation period from 1981 to 1994 (Table 2). Second, the annual incidence of another childhood cancer — namely, brain tumors in children of the same age — remained similar during the same period. The incidence of liver cancer in children younger than six years also did not decrease. This suggests that the decrease in childhood hepatocellular carcinoma is specific. Third, the incidence of hepatocellular carcinoma decreased in children but gradually increased in people older than 14 years between 1981 and 1993. The increase in incidence in adults is reasonable, since diagnostic accuracy has improved and screening programs using ultrasonography and alpha-fetoprotein have been launched for early detection of liver cancer in high-risk subjects.<sup>6</sup> The increasing life span of the population and the growing role of hepatitis C virus<sup>18</sup> may also contribute to the increase of liver cancer in adults.

A decline in the incidence of liver cancer has been observed since 1986 among children 6 to 14 years old who were born between 1980 and 1984, before the start of the national vaccination program. This decline is paralleled by a decrease in the rate of HBsAg carriage among children born before the program was launched (Table 1). The herd immunity resulting from the mass vaccination of children in the highly infectious younger birth cohorts may have reduced the rate of horizontal HBV infection among unvaccinated older children. The reduction in the HBsAg-seropositivity rate among children in

unvaccinated cohorts reflects a decline of a similar magnitude in the incidence of hepatocellular carcinoma. The decline in incidence among children born before the launch of the national vaccination program may be attributable to the herd immunity resulting from the program. The extension of the vaccination program to preschool children might also have contributed to the decline in the rate of HBsAg carriage and in the rate of hepatocellular carcinoma in children born before July 1984.

Perinatal mother-to-infant transmission of HBV is an important factor in the rate of HBsAg carriage. It accounts for 40 to 50 percent of HBsAg carriers in Taiwan.<sup>19</sup> These perinatally infected HBsAg carriers are at risk for hepatocellular carcinoma as adults<sup>20</sup> or children.<sup>7,8</sup> The HBsAg-positivity rate has been shown to be as high as 94 percent among the mothers of children with hepatocellular carcinoma in Taiwan.<sup>7</sup> Similarly, perinatal transmission of woodchuck hepatitis virus has been reported to cause liver cancer.<sup>5</sup>

The Taiwanese program of vaccination to reduce the perinatal transmission of HBV has been carried out successfully since 1984. According to our previous observations in Taiwan,<sup>7,8,14</sup> the earliest time at which the effect of the hepatitis B vaccination program on childhood hepatocellular carcinoma can be seen is 1990, six years after the launch of the program. If the efficacy of the program were 100 percent, with a coverage of 100 percent, and childhood hepatocellular carcinoma were caused solely by HBV, there should be no hepatocellular carcinoma in children born after July 1984. Children who missed the vaccination program or failed to respond to the vaccine could still have hepatocellular carcinoma later on. In fact, hepatocellular carcinoma was found in three children who were born after July 1984 and had received hepatitis B immunization through the national program. The effect of HBV vaccination on the declining incidence of childhood hepatocellular carcinoma was most evident when different birth cohorts were analyzed (Table 4).

This HBV vaccination program has been integrated into the Expanded Programme on Immunization for Taiwanese infants since July 1986. We strongly recommend that hepatitis B vaccination be integrated into the worldwide Expanded Programme on Immunization to interrupt perinatal and early horizontal transmission of HBV and the subsequent development of chronic liver disease. Such measures are important and urgent, particularly in areas with a high incidence of HBV infection and hepatocellular carcinoma.

Since HBV-associated liver cancer peaks among people 50 to 60 years of age in Taiwan,<sup>6</sup> continued monitoring of the incidence of hepatocellular carcinoma among children and adults is necessary to further document the decrease in cases of hepatocellular carcinoma in association with the initiation of the hepatitis B mass-vaccination program.

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## APPENDIX

The following additional institutions and investigators participated in the Taiwan Childhood Hepatoma Study Group: C.-S. Chi, *Veterans General Hospital, Taichung*; S.-N. Cheng, *Tri-Service General Hospital*; C.-J. Tsai, *Kaohsiung Medical College*; L.-H. Lin, *Cathay General Hospital*; M.-W. Lai, *Taoyuan Provincial Hospital*; M.-T. Cheng, *Chang-hua Christian Hospital*; A.-C. Chen, *National Cheng-Kung University Hospital*; W.-C. Lee, *Sa-lu Kong-Ten General Hospital*; T.-C. Tsai, *Hua-lien Tzu-Chi Buddhist Hospital*; Y.-H. Tsai, *Taiwan Provincial Taipei Hospital*; C.-C. Wu, *St. Mary's Hospital*; S.-F. Wu, *China Medical College Hospital*; S.-C. Huang, *Chang-Gung Children's Hospital, Kaohsiung*; and U.-P. Ling, *Chung-Shan Medical College Hospital*.

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