patients at 15–49 years old comprised 21%, while patients over 50 years old made up 62%, meaning that the rate in aged patients was 3.0 times higher than in those of a younger age.

In female patients, the age-specific distribution of ITP patients appeared to have a trimodal distribution, with the first peak observed below 4 years, the second among those aged 20–34 years, and the third peak among those aged 50–89 years (Fig. 1). On the other hand, the highest peak of the number of patients was among those aged 55–59 years (Fig. 2). Female patients aged 15–49 years old comprised 35%, while patients over 50 years old made up 56%.

The number of ITP patients differed greatly between males and females. The F/M ratio in children below 4 years was 0.69. The incidence of ITP among boys below 4 years was higher compared to girls. However, for children in the older age groups, the pattern was reversed, with a lower incidence among boys compared to girls. In patients aged 15–49 and over 50 years old, the F/M ratios were 2.62 and 1.39, respectively. The sex difference was eliminated in patients at 65–74 years old, and then there was a marked predominance of male patients.

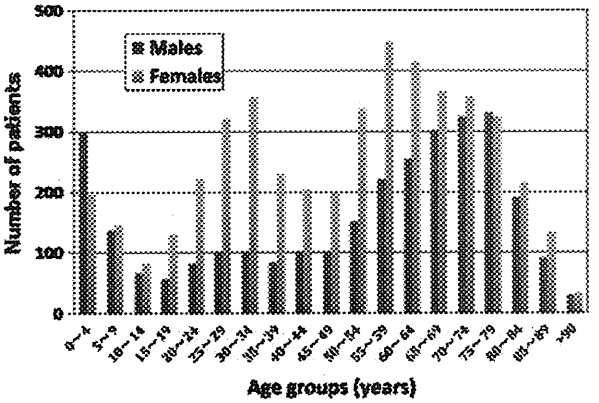

Fig. 2 Age and sex distribution of ITP patients

3.3 Platelet counts

The platelet count for each patient was the lowest for 6 months before application. The frequency distribution of platelet counts is shown in Fig. 3. The mean platelet count was 22.0 $\times$ 10^9/L in the total ITP patients (23.7 in females and 19.3 in males), 12.8 $\times$ 10^9/L in patients less than 15 years old, 27.2 $\times$ 10^9/L at 15–49 years old, and 21.1 $\times$ 10^9/L in patients more than 50 years old. Sixty-two percent of child patients had a platelet count of less than 10 $\times$ 10^9/L. This percentage is significantly higher ($p < 0.001$) than that (41.2%) in adult patients.

3.4 Hemorrhagic symptoms

The presenting clinical features are shown in Table 2. The most common presenting symptom was purpura (overall, 66.4%). The frequency of purpura (92.6%) and epistaxis (29.7%) in child ITP patients was significantly higher than that of purpura (62.8%) and epistaxis (10.0%) in adult patients. Cerebral vascular bleeding was noted as one of the presenting symptoms in 46 patients; one of these patients was a child, and the other 45 were adults.

3.5 Therapy

Therapies for child and adult ITP patients are summarized in Table 3. Therapies were significantly different between the child and adult patients. Two-thirds of child ITP patients received high-dose IgG therapy. In contrast, only 1,118 (16.3%) of adult ITP patients received such therapy. Prednisolone and the eradication of *Helicobacter pylori* in adult ITP patients were significantly higher (64.0 and 27.4%, respectively) compared with those in child ITP patients (44.0 and 1.9%, respectively). Approximately one-fifth of adult ITP patients received no medical therapy.

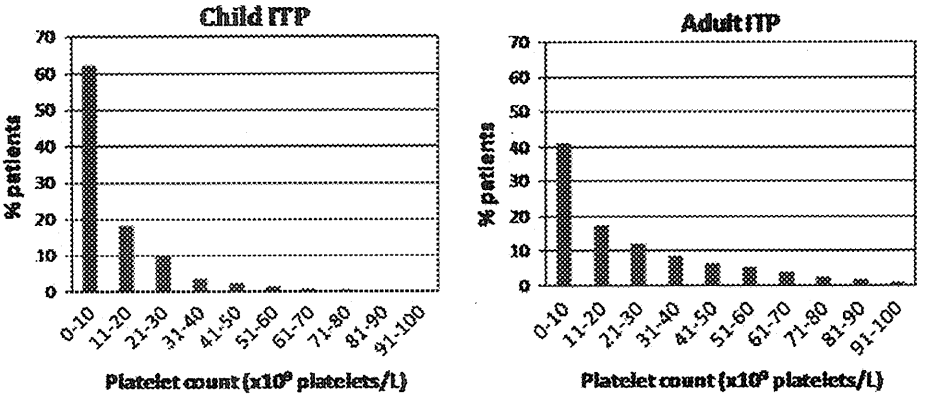

Fig. 3 Frequency distribution of the platelet counts in child and adult ITP patients

Table 2 Hemorrhagic symptoms of child and adult ITP

Bleeding symptoms	Overall (7,774 cases) Number of cases (%)	Child (929 cases) Number of cases (%)	Adult (6,845 cases) Number of cases (%)	*p* value (Child vs. adult)
Purpura	5,160 (66.4)	860 (92.6)	4,300 (62.8)	$p < 0.001$
Gingival bleeding	1,540 (19.8)	175 (18.8)	1,365 (19.9)	ns
Epistaxis	963 (12.4)	276 (29.7)	687 (10.0)	$p < 0.001$
Hematuria	507 (6.5)	54 (5.8)	453 (6.6)	ns
Melena	302 (3.9)	43 (4.6)	259 (3.8)	ns
Hypermenorrhea	275 (3.5)	11 (1.2)	264 (3.9)	$p < 0.001$
Cerebral bleeding	46 (0.6)	1 (0.1)	45 (0.7)	$p < 0.05$
Other bleeding	268 (3.4)	54 (5.8)	214 (3.1)	$p < 0.001$

ns not significant

Table 3 Therapy for child and adult ITP

Treatment	Overall (7,774 cases) Number of cases (%)	Child (929 cases) Number of cases (%)	Adult (6,845 cases) Number of cases (%)	*p* value (Child vs. adult)
Prednisolone	4,793 (61.7)	409 (44.0)	4,384 (64.0)	<0.001
Eradication of *H. pylori*	1,895 (24.4)	18 (1.9)	1,877 (27.4)	<0.001
High-dose IgG	1,731 (22.3)	613 (66.0)	1,118 (16.3)	<0.001
Splenectomy	233 (3.0)	5 (0.5)	228 (3.3)	<0.001
Immunosuppressant	172 (2.2)	6 (0.6)	166 (2.4)	<0.001
Danazol	117 (1.5)	4 (0.4)	113 (1.7)	<0.005
No therapy	1,643 (21.1)	129 (13.9)	1,514 (22.1)	<0.001

Table 4 Incidence of patients with ITP (All ages)

Study (year)	Number of patients	Design	Country	Annual population base	Inclusion criteria	Incidence (year studied)
Takahashi et al. [9]	523	Retrospective by registered data	Japan	ND	Plt. count $<100 \times 10^9$/L	2.28 (2001–2002)
Schoonen et al. [11]	1,145	Retrospective by administrative data	England	1.2–2.3 million	Plt. count: ND	3.9 (1990–2005)
This study (2010)	7,774	Retrospective by registered data	Japan	90.0 million	Plt. count $<100 \times 10^9$/L	2.16 (2004–2007)

ND not described; *plt. count* platelet count

4 Discussion

4.1 Incidence rate

We identified an annual incidence of 2.16 per 100,000 persons in all ages, as well as 1.91 in child and 2.20 in adult ITP patients. Tables 4, 5, 6 show the incidence reported in the literature [3–12]. Table 4 presents the incidence of ITP patients (all ages) [9, 11], and Tables 5 [3–5, 7, 10] and 6 [6, 8, 12] show the incidence of ITP in children and adults, respectively. In these reports, the number of ITP patients and/or size of the population was very small compared with our reports. Our report is, to date, the largest one.

There are several reasons why the incidence varies widely across studies. The first is the inclusion criteria used to define an ITP case, especially the cut-off point of the platelet count. Some investigators [8, 10] used less than 50×10^9/L or 30×10^9/L as inclusion criteria because these platelet counts are threshold points for clinically meaningful bleeding, and the others [6, 9] used 100×10^9/L or 150×10^9/L. It is expected that there would be a marked difference in the incidence depending on whether they use a low or high platelet count as inclusion criteria. A recently published report [14] from an International Working Group recommends the platelet count to be less than 100×10^9/L as the threshold for diagnosis. Therefore, we consider that it is necessary to report epidemiologic data using 100×10^9/L as a cut-off point for the platelet count in ITP.

The second reason is that different study designs have been utilized in these studies and there was a marked difference in the method regarding how to search the records of ITP patients. Terrell et al. [15] reported a critical review of published reports on the incidence of ITP. Some

Table 5 Incidence of child ITP patients

Study (year)	Number of patients	Design	Country	Annual population base	Inclusion criteria	Incidence (year studied)
Zaki et al. [3]	60	Retrospective by clinical criteria	Kuwait	0.125 million	Below 14 years Plt. count: ND	12.5 (1981–1986)
Lilleyman [4]	70	Prospective by clinical criteria	England	0.48 million	Below 14 years Plt. count: ND	4.8 (1980–1994)
Bolton-Maggs et al. [5]	427	Prospective by questionnaire	England	13 million	Below 15 years Plt. count: ND	3 (1995–1996)
Zeller et al. [7]	92	Prospective by registered data	Norway	0.86 million	Below 14 years Plt. count: ND	5.3 (1996–1997)
Zeller et al. [10]	506	Prospective by questionnaire	Nordic	4.6 million	Below 14 years Plt. count $<30 \times 10^9$/L	4.8 (1998–2000)
This study (2010)	929	Retrospective by registered data	Japan	12.2 million	Below 14 years Plt. count $<100 \times 10^9$/L	1.91 (2004–2007)

ND not described, *plt. count* platelet count

Table 6 Incidence of adult ITP patients

Study (year)	Number of patients	Design	Country	Annual population base	Inclusion criteria	Incidence (year studied)
Frederiksen et al. [6]	221	Retrospective by ICD code	Denmark	0.368 million	More than 15 years old Plt. count $<100 \times 10^9$/L	2.68 (1973–1995)
Neylon et al. [8]	245	Prospective by clinical criteria	England	3.08 million	More than 16 years old Plt. count $<50 \times 10^9$/L	1.6 (1993–1999)
Abrahamson et al. [12]	840	Retrospective by administrative data	England	1.55 million	More than 18 years old Plt. count: ND	3.9 (1992–2005)
This study (2010)	6,845	Retrospective by registered data	Japan	77.8 million	More than 15 years old Plt. count $<100 \times 10^9$/L	2.20 (2004–2007)

ND not described, *plt. count* platelet count

investigators analyzed the ITP patients seen in their hospital retrospectively [3] or in their region prospectively [4, 8]. These studies apparently include all newly diagnosed ITP patients. However, the numerator only included patients seen at one hospital or in one region. Other investigators sent questionnaires to pediatricians and hematologists in their regions to assess whether or not they had seen new patients presenting with ITP [5, 10]. The accuracy of active surveillance using a questionnaire depends on the response rate. A low response rate could have resulted in an underestimation of the incidence of ITP. However, we and other investigators [6, 7, 9, 11, 12] performed a prospective or retrospective cohort analysis of patients registered in the data bank. The diagnosis of ITP was based on administrative or discharge codes [11, 12] without a chart review to validate the diagnosis. Segal et al. [16] reported that estimation of the prevalence of ITP using the coding system was not so accurate, particularly when outpatient data were used. In our study, the initial diagnosis of ITP in the health care system for intractable diseases in Japan is rather accurate, since the hematological data including bone marrow examination are further validated by the Committee of the Department of Health and Medical Care of the regional prefecture.

Our study has some limitations as well. Firstly, our registration system is not mandatory. ITP patients themselves apply for recognition of the specified disease to the Department of Health and Medical Care of the regional prefecture according to their physician's advice. Some patients do not apply because they do not want to receive financial support or the disease status is mild. In this case, the incidence might be underestimated. Secondly, some possibilities exist that thrombocytopenic patients except those with ITP apply to obtain financial support. Aplastic anemia is already recognized as a specified disease in Japan. However, myelodysplastic syndrome is not recognized as a specified disease. Therefore, patients with myelodysplastic syndrome may apply for specified disease recognition. In this case, the incidence might be overestimated. The Committee of the Department of Health and

Medical Care of the regional prefecture check the hematological data, especially the differential count of peripheral white blood cells, and the results of bone marrow examination. They reject the application if myelodysplastic syndrome or other thrombocytopenic disorders cannot be excluded.

4.2 Age and sex distribution

Our data show a male preponderance among pediatric ITP patients among children aged 4 years or younger. These findings are in line with earlier reports [10, 17–19] of a male preponderance in early childhood ITP and male-to-female ratios decreasing from infancy to adolescence.

It has previously been reported that most cases of ITP occur between 20 and 40 years old, and that it is less common after 50 years old. We identified an increasing annual ITP incidence with age. The maximum age-specific incidence was in the eighth decade. This is in contradiction to the generally accepted epidemiological data [19, 20]. The observed findings regarding the ITP incidence by age in this study were similar to those of previous studies reported by Neylon et al. [8] and Frederiksen et al. [6], whereby both the groups estimated a higher incidence of ITP among those aged 60 years and older. These changes may reflect the changing age profile of the general population.

The incidence among both men and women began to increase after the age of 50. The incidence among women was higher than in men until 65, but not thereafter; there was no gender-specific relative differences in the age group of 65–74 years old. Schoonen et al. [11] also reported similar data. Of special interest is that gender-specific relative differences shifted to men with a higher incidence than women in the 75-year-old and older age groups. There are no reports that men show a higher incidence than women in the 75-year-old and older age groups.

4.3 Platelet counts and hemorrhagic symptoms

The platelet count in child ITP was very low compared with that in adult ITP (Fig. 3). Especially, the frequency of cases with a platelet count of 10,000 or less was high in child ITP. It is well-known that the platelet count is very low in patients with acute ITP. The platelet count in child ITP may be low since the major form of ITP in childhood is acute ITP [20].

The frequency of purpura and nasal bleeding in child ITP was significantly higher than in adult ITP. We considered that this also reflected the result that the acute form of ITP is frequent in childhood, as mentioned above [20]. On the other hand, the frequency of cerebral bleeding in patients with adult ITP was very high. This suggests that cases of cerebral bleeding might increase with the advancing age of patients with ITP.

4.4 Therapy

A variety of therapies were performed for ITP patients. Patients who received no treatment comprised 1.39% of those with child ITP, and 22.1% of those with adult ITP. The most frequently performed therapy for child ITP was high-dose IgG therapy, and 66.0% of child patients received this therapy. Several explanations may be considered: (1) the dosage of IgG in childhood may be low, so the cost would be cheaper than for adult ITP, (2) acute ITP is the major form in childhood, and this form involves serious hemorrhagic symptoms [20], so a rapid rise in the platelet count may be needed. Recently, in Japan, therapy involving the eradication of *Helicobacter pylori* has become widespread, and this study revealed that 27.4% of adult ITP patients received this therapy. There is convincing evidence [21] that the eradication of *Helicobacter pylori* is very effective to treat adult ITP patients, especially in Japan and Italy.

In summary, our report provides a population-based estimate of the incidence of ITP in Japan. The overall incidence was 2.16 per 10^5 per annum. This study is the largest reported to date. This population-based study suggests that the incidence of ITP increases with age, showing a biphasic distribution, with most patients presenting during the seventh and eighth decades, suggesting that the traditional view of adult ITP as being a disease that affects predominantly young females needs to be modified.

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