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Incidence and In-Hospital Mortality of Neonatal Disseminated Intravascular Coagulation in Japan: An Observational Study of a Nationwide Hospital Claims Database

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Abstract **:** This study aimed to estimate the incidence and prognosis of neonatal disseminated intravascular coagulation (DIC) in Japan by analyzing data retrieved from a national administrative database. Clinically, the prognosis of DIC in neonates is poor, but there is little epidemiological data in Japan. This retrospective observational study identified patients diagnosed with neonatal DIC and who were registered in the Japanese diagnosis procedure combination (DPC) database between April 1, 2014 and March 31, 2016. The patients, who were diagnosed with neonatal DIC, included those with ICD-10 code D65 or P60 in primary and secondary diagnosis, with comorbid conditions existing at admission, and with complications occurring after admission. Of 78,073 neonates admitted to 1,474 neonatal intensive care units, 1,864 (2.4%) were diagnosed with DIC. There was no difference between sexes in incidence of DIC; the incidence of DIC was higher in extremely low birth weight infants (9.8%), and significantly higher than that in normal birth weight infants. The overall mean length of hospital stay was longer in neonates with DIC (69.5 days) than in those without DIC (32.6 days, $P < 0.001$). The number of deaths was 1,156 (1.5%). In-hospital mortality was significantly higher in neonates with DIC (14.1%) than in those without DIC (1.2%, $P < 0.001$), especially in premature babies. This nationwide study was the first report to investigate the incidence and in-hospital mortality of neonatal DIC in Japan. Neonatal DIC has a significant impact on prognosis, and its influence is greater in premature than in term infants.

Keywords **:** in-hospital mortality, length of hospital stay, morbidity rate, neonates, DIC.

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Introduction

Disseminated intravascular coagulation (DIC) is a serious, acquired clinical condition in which the activation of hemostasis results in excessive thrombin production and microvascular obstruction [1, 2]. DIC may be present in patients with infections and septic shock and requires prompt diagnosis and treatment of both the coagulation disorder and the underlying disease. It has been widely described in pediatric and neonatal populations, but there are few clinical studies that report its incidence and prognosis in these populations worldwide because of the difficulty of diagnostic testing [1]. We used the specific guidelines and diagnostic criteria for neonatal DIC [2−4]. Neonatologists in Japan diagnose neonatal DIC according to these specific diagnostic criteria.

The Japanese case-mix classification system, including a diagnosis–procedure combination (DPC) database, was introduced in 2003 and is used to standardize medical profiling and payment [5, 6]. DPC hospitals that participate in the DPC project have been increasing, and the number of the hospitals reached 1,664 in 2017. The system collects annual inpatient data covering approximately 55.4% of all the inpatient beds in Japan and is representative of the status of medical care in Japan at the national population level. The data are coded using the International Classification of Diseases, tenth revision (ICD-10). Neonatologists routinely enter diagnoses in the patient medical records, and the use of the DPC data in clinical reports involving diverse medical specialties has been increasing [7−12], but there have been no previous studies on neonatal DIC using the DPC database in Japan. The aim of this retrospective study was to estimate the incidence and prognosis of neonatal DIC in Japan by analyzing the data available in the national administrative DPC database.

Methods

Data source

The Ministry of Health, Labor and Welfare (MHLW) of Japan initiated and has been responsible for the original case-mix program, that is, the DPC project, since 2003. The MHLW gathers DPC-related data from all the institutions that currently participate in and administer the database. The DPC contains clinical and medical claims data of delivery date, cost, and quantities of medical resources. In addition to the MHLW activity, the DPC Research Institute facilitates the use of patient data in health research by making ICD-10 codes for primary and secondary diagnosis, comorbid conditions existing at admission, and complications occurring after admission; these codes are available to investigators. The present study evaluated inpatient data for the 24 months between April 1, 2014 and March 31, 2016. The study protocol was approved by the Ethics Committee of Medical Care and Research of the University of Occupational and Environmental Health, Japan.

Patient selection and outcomes

The DPC data from 78,073 neonates included 11,908 very low birth weight infants (VLBWIs) who were admitted to neonatal intensive care units (NICUs) in 1,474 of the 1,667 participating institutions, representing 88.4% of all DPC hospitals as of April 2016. The sample of patients included those who were diagnosed with neonatal DIC (ICD-10 code D65 or P60) in primary and secondary diagnosis, with comorbid conditions existing at admission, and with complications occurring after admission. The variables extracted from the DPC database included sex, birth weight, gestational age, status at discharge, and length of hospital stay (LOS). Using these data, we examined 1: status of incidence of neonatal DIC, and 2: whether LOS and in-hospital death were affected by 1) sex, 2) birth weight, and 3) gestational age.

Statistical analysis

The chi-square test for categorical data was used to compare differences in the numbers of neonates with DIC. The Mann–Whitney U test was used to compare differences in continuous variables. Multiple logistic regression models were used to estimate the odds ratios (ORs) and their 95% confidence intervals (CIs) for DIC-associated death. Statistical analysis was performed by Stata 15.1 (Stata Corporation, College Station, TX, USA). P-values < 0.05 were considered to be statistically significant.

Results

Incidence and morbidity of neonatal DIC

Of the 78,073 neonates who were admitted to the participating NICUs during the study period, 1,864 (2.4%) were diagnosed with DIC. There were no significant differences in the diagnosis between male and female neonates (Table 1). DIC was diagnosed in 706 of the 11,908 VLBWIs (5.9%) with birth weight < 1,500 g . The DIC morbidity rate in extremely low birth weight infants (ELBWIs) with birth weight < 1,000 g was 9.8% and was significantly higher than that in other birth weight groups ($P < 0.001$). Premature infants with a gestational age of < 28 weeks had the highest DIC morbidity compared with other gestational ages ($P < 0.001$).

Length of hospital stay (LOS)

The LOS data of the study population are shown in Table 2. There were no sex-related differences in the LOS, but birth weight and gestational age influenced the LOS. The mean overall LOS in neonates with DIC (69.5 days) was significantly longer than that in neo-

Table 1. The incidence of neonatal DIC

	Total n	DIC n (%)	*P*-value*
Overall	78,073	1,864 (2.4)	
Sex			
male	42,450	1,003 (2.4)	
Female	35,623	861 (2.4)	
			0.621
Birth weight (g)			
<1000	5,042	493 (9.8)	
1000−1499	6,866	213 (3.1)	
1500−2499	32,723	413 (1.3)	
≥2500	33,442	745 (2.2)	
			<0.001
Gestational age (weeks)			
<28	4,196	427 (10.2)	
28−32	7,046	285 (4.0)	
33−36	20,951	260 (1.2)	
≥37	45,880	892 (1.9)	
			<0.001

*Chi-square test. Data are number (%). DIC: disseminated intravascular coagulation

Table 2. Length of hospital stay by neonates with and without DIC

	All			*P*-value*	Excluding death cases			*P*-value*
	Total	DIC (+)	DIC (−)		Total	DIC (+)	DIC (−)	
Overall	33.5	69.5	32.6	<0.001	32.8	73.4	32.0	<0.001
Sex								
male	32.9	73.8	31.9	<0.001	32.4	77.1	31.4	<0.001
female	34.2	64.4	33.4	<0.001	33.4	68.9	32.6	<0.001
Birth weight (g)								
<1000	113.0	119.0	112.3	0.052	117.9	140.0	115.8	<0.001
1000−1499	66.3	79.5	65.9	<0.001	66.2	88.3	65.6	<0.001
1500−2499	30.8	55.5	30.5	<0.001	30.1	55.3	29.8	<0.001
≥2500	17.3	41.6	16.8	<0.001	17.0	40.0	16.5	<0.001
Gestational age (weeks)								
<28	115.1	119.8	114.5	0.18	121.3	145.4	119.0	<0.001
28−32	70.2	86.4	69.6	<0.001	70.2	94.1	69.3	<0.001
33−36	34.4	60.6	34.1	<0.001	34.0	60.8	33.8	<0.001
≥37	19.9	42.6	19.5	<0.001	19.2	41.2	18.8	<0.001

*DIC (+) vs DIC (−), Mann–Whitney U test. Data are average days. DIC: disseminated intravascular coagulation, DIC (+): with DIC, DIC (−): without DIC

nates without DIC (32.6 days, $P < 0.001$). Exceptionally, there were no significant differences in either the LOS of ELBWI neonates weighing < 1,000 g or that of premature neonates with a gestational age of < 28 weeks who were affected by the presence of DIC. When the neonates who died were excluded from the analysis, however, the mean LOS of neonates without DIC was significantly shorter than that of neonates with DIC, regardless of sex, gestational age, and birth weight.

Incidence of in-hospital death

The number of deaths at discharge during the study period was 1,156 (1.5%). The mortality of neonates with DIC was 14.1%, which was significantly higher than that of neonates without DIC (1.2%, Table 3). The mortality of premature infants with DIC (gestational age of < 28 weeks) was higher than that of term infants with DIC. The results of multiple logistic regression analysis for in-hospital death are shown in Table 4. In model one, which included DIC, sex, and Birth weight (BW) as the variables, DIC was independently associated with in-hospital death (OR = 8.34; 95% CI = 7.11−9.78) and low birth weight. In model two, DIC, sex, and gestational age were independently associated with in-hospital death (DIC: OR = 8.34; 95% CI = 7.12–9.77, Sex: OR = 1.17; 95%CI = 1.04−1.32, Gestational age: OR = 7.57; 95% CI = 6.55−8.76). The probability of in-hospital death of neonates with a gestational age of 33−36 weeks was lower than that of neonates with a gestational age of ≥ 37 weeks (OR = 0.87, 95% CI = 0.73−1.03).

Discussion

This study reports epidemiological data of neonatal DIC in Japan extracted from an administrative database representative of the national population. There are several key findings in this study. First, the overall incidence of neonatal DIC in Japan in the 24 months between April 1, 2014 and March 31, 2016 was 2.4%; second, neonatal DIC significantly influenced LOS and in-hospital mortality; and third, birth weight and gestational age were independently associated with morbidity and mortality in neonates with DIC.

A cohort of 11,908 VLBWIs included in the analysis had a 2-year morbidity of neonatal DIC of 5.9%. Approximately 10,000 VLBWIs were estimated to have been born annually in Japan between 2003 and 2008 [13]. Our study population thus covered about half of the VLBWIs born in Japan during the study period. The large number of patients enrolled is a strength of this study.

To our knowledge, there have been no previous large epidemiological studies of neonatal DIC. Neonates are postulated to be more susceptible to DIC than older infants and children [14]. Previous studies of incidences of DIC in pediatric populations between 1 month and 18 years of age have reported that 1.12% of such cases are associated with infection and major trauma [1], 14% with childhood lymphoblastic leukemia [15], and 4−8% with acute promyelocytic leukemia [16]. Differences in the incidence of DIC might reflect differences in etiology associated with the underlying disorders and difficulties in diagnosing DIC. Dairaku *et al* reported that only one of 24 neonates histopathologically confirmed to have DIC was diagnosed clinically before death [17].

The present study also found that DIC significantly influenced the mortality and LOS of neonates. Even though the development of DIC in neonates has been thought to be clinically fatal, there is little epidemiological data in Japan. This study showed that neonates with DIC have a twice longer LOS (69.5 days vs 32.6 days, $P < 0.001$) and ten times higher in-hospital mortality (14.1% vs. 1.2%, $P < 0.001$) than neonates without DIC.

The other key finding was that the mortality of neonates with DIC was significantly influenced by birth weight and gestational age. The mortality rate of ELWBIs with DIC (20.7%) was about twice as high as that of normal birth weight infants (≥2,500g) with DIC (9.9%). Additionally, the multiple logistic regression analysis revealed that birth weight and gestational age were independently associated with in-hospital death. Previous reports have shown that the mean levels of many coagulation and anticoagulation factors were significantly lower in preterm than in term infants [3, 18, 19], and that differences resulting from the immaturity of organ function in preterm infants led to coagulopathy. Those reports are in line with the findings of this study and indicate that neonatologists should carefully evaluate the coagulation status of preterm infants.

Table 3. Mortality of neonates with and without DIC

	Total Death N (%)	DIC (+)		DIC (−)		*P*-value*
		Death/N	%	Death/N	%	
Overall	1,156 (1.5)	262/1,864	14.1	894/76,209	1.2	<0.001
Sex						
male	588 (1.4)	135/1,003	13.5	453/41,447	1.1	<0.001
female	568 (1.6)	127/ 861	14.8	441/34,762	1.3	<0.001
Birth weight (g)						
<1000	431 (8.6)	102/ 493	20.7	329/ 4,549	7.2	<0.001
1000−1499	138 (2.0)	27/ 213	11.3	111/ 6,653	1.7	<0.001
1500−2499	341 (1.0)	59/ 413	14.3	282/32,310	0.9	<0.001
≥2500	246 (0.7)	74/ 745	9.9	172/32,697	0.5	<0.001
Gestational age (weeks)						
<28	392 (9.3)	98/ 427	23.0	294/ 3,769	7.8	<0.001
28−32	132 (1.9)	41/ 285	14.4	91/ 6,761	1.4	<0.001
33−36	174 (0.8)	38/ 260	14.6	136/20,691	0.7	<0.001
≥37	458 (1.0)	85/ 892	9.6	373/44,988	0.8	<0.001

*DIC (+) vs D3C (−), chi-square test. Data are number (%). DIC: disseminated intravascular coagulation, DIC (+): with DIC, DIC (−): without DIC

Table 4. Multivariable logistic regression analysis of in-hospital death

	Model 1 †			Model 2 ‡		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
DIC (+)	8.34	7.11−9.78	<0.001	8.34	7.12−9.77	<0.001
DIC (−) (ref.)						
Sex						
Male (ref.)						
Female	1.10	0.97−1.24	0.12	1.17	1.04−1.32	0.011
Birth weight						
<1000	9.55	8.10−11.3	<0.001			
1000−1499	2.64	2.14−3.27	<0.001			
1500−2499	1.50	1.27−1.77	<0.001			
≥2500 (ref.)						
Gestational age (weeks)						
<28				7.57	6.55−8.76	<0.001
28−32				1.68	1.38−2.05	<0.001
33−36				0.87	0.73−1.03	0.108
≥37 (ref.)						

OR: odds ratio, CI: confidence intervals. †Model 1 included DIC, sex, and birth weight. ‡Model 2 included DIC, sex, and gestational age

This study has some limitations. First, as the DPC does not include laboratory data consistent with a diagnosis of DIC, its severity and underlying etiology could not be determined. Further, DPC was sometimes associated with drugs the doctor used. Therefore, analysis of data from a comprehensive, disease-specific registry would be preferable in future studies. Secondly, we could not confirm a direct relationship between in-hospital death and neonatal DIC. Thirdly, this study does not cover all of the participating DPC hospitals; it includes data obtained only from the participating hospitals contracted to the DPC Research Institute, not all medical institutions in Japan.

In conclusion, this nationwide study estimated the incidence of neonatal DIC and in-hospital mortality in neonates with DIC in Japan. The study, using national administrative database, shows for the first time that neonatal DIC has a significant impact on prognosis, and its influence is greater in premature than in term infants.

Conflict of Interest

The authors have no conflicts of interest to disclose.

References

1. Oren H, Cingöz I, Duman M, Yilmaz S & Irken G (2005): Disseminated intravascular coagulation in pediatric patients: Clinical and laboratory features and prognostic factors influencing the survival. Pediatr Hematol Oncol 22: 679–688
2. Wada H, Matsumoto T & Yamashita Y (2014): Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. J Intensive Care 2: 15
3. Rajagopal R, Thachil J & Monagle P (2017): Disseminated intravascular coagulation in paediatrics. Arch Dis Child 102: 187–193
4. Shirahata A, Shirakawa Y & Murakami C (1998): Diagnosis of DIC in very low birth weight infants. Semin Thromb Hemost 24: 467–471
5. Fushimi K, Hashimoto H, Imanaka Y, Kuwabara K, Horiguchi H, Ishikawa KB & Matsuda S (2007): Functional mapping of hospitals by diagnosis-dominant case-mix analysis. BMC Health Serv Res 7: 50
6. Yasunaga H, Matsui H, Horiguchi H, Fushimi K & Matsuda S (2014): Application of the diagnosis procedure combination (DPC) data to clinical studies. J UOEH 36: 191–197
7. Kido T, Muramatsu K, Asakawa T *et al* (2018): The relationship between high-dose corticosteroid treatment and mortality in acute respiratory distress syndrome: A retrospective and observational study using a nationwide administrative database in Japan. BMC Pulm Med 18: 28
8. Murata A, Okamoto K, Mayumi T, Muramatsu K & Matsuda S (2015): Observational study to compare antithrombin and thrombomodulin for disseminated intravascular coagulation. Int J Clin Pharm 37: 139–147
9. Tagami T, Matsui H, Horiguchi H, Fushimi K & Yasunaga H (2015): Recombinant human soluble thrombomodulin and mortality in severe pneumonia patients with sepsis-associated disseminated intravascular coagulation: An observational nationwide study. J Thromb Haemost 13: 31–40
10. Tagami T, Matsui H, Horiguchi H, Fushimi K & Yasunaga H (2014): Antithrombin and mortality in severe pneumonia patients with sepsis-associated disseminated intravascular coagulation: An observational nationwide study. J Thromb Haemost 12: 1470–1479
11. Taniguchi Y, Oichi T, Ohya J, Chikuda H, Oshima Y, Matsubayashi Y, Matsui H, Fushimi K, Tanaka S & Yasunaga H (2018): In-hospital mortality and morbidity of pediatric scoliosis surgery in Japan: Analysis using a national inpatient database. Medicine (Baltimore) 97: e0277
12. Michihata N, Matsui H, Fushimi K & Yasunaga H (2016): Hospital volume and mortality due to preterm patent ductus arteriosus. Pediatr Int 58: 1171–1175
13. Kusuda S, Fujimura M, Uchiyama A, Totsu S & Matsunami K; Neonatal Research Network, Japan (2012): Trends in morbidity and mortality among very-low-birth-weight infants from 2003 to 2008 in Japan. Pediatr Res 72: 531–538
14. Veldman A, Fischer D, Nold MF & Wong FY (2010): Disseminated intravascular coagulation in term and preterm neonates. Semin Thromb Hemost 36: 419–428
15. Higuchi T, Toyama D, Hirota Y, Isoyama K, Mori H, Niikura H, Yamada K & Omine M (2005): Disseminated intravascular coagulation complicating acute lymphoblastic leukemia: A study of childhood and adult cases. Leuk Lymphoma 46: 1169–1176

16. Ribeiro RC & Rego E (2006): Management of APL in developing countries: Epidemiology, challenges and opportunities for international collaboration. Hematology Am Soc Hematol Educ Program: 162−168
17. Dairaku M, Sueishi K & Tanaka K (1982): Disseminated intravascular coagulation in newborn infants. Prevalence in autopsies and significance as a cause of death. Pathol Res Pract 174: 106−115
18. Ochiai M, Matsushita Y, Inoue H *et al* (2016): Blood reference intervals for preterm low-birth-weight infants: A multicenter cohort study in Japan. PLoS One 11: e0161439
19. Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, Castle V & Powers P (1988): Development of the human coagulation system in the healthy premature infant. Blood 72: 1651−1657

DPCデータを用いた日本における新生児DICの発生と院内死亡率

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要　　旨：日本における新生児播種性血管内凝固症候群（disseminated intravascular coagulation: DIC）の発生率は不明であり，今回われわれは診断群分類（diagnosis procedure combination: DPC）データを用いてわが国における新生児DICについての疫学研究を行った．診断群分類研究機構にデータが提出されている1,474施設に2014年4月1日から2016年3月31日の間に入院し，入院時年齢が0歳かつ新生児特定集中治療室管理料を算定している児を対象とした．「主傷病名」，「入院の契機となった傷病名」，「最も医療資源を消費した傷病名」，「2番目に医療資源を消費した傷病名」，「入院時併存症」，「入院後発症病名」のいずれかにinternational classification of disease（ICD）-10上で播種性血管内凝固（D65），新生児播種性血管内凝固（P60）が登録されている症例を抽出した．78,073例が対象となり，新生児DICの発生数は1,864例，発生率は2.4%であった．男女差は認めなかった．出生体重別では1,000 g未満では9.8%と有意に高く，在胎期間別の検討で28週未満では10.2%がDICを発症していた．DICを発生した症例の平均在院日数は69.5日とDICを発症しなかった症例の32.6日と比較して有意に延長していた．全死亡数は1,156例（1.5%），DIC発症群では262例/1,864例（14.1%）で，DIC非発症群の894例/76,209例（1.2%）に比較して有意に院内死亡率が高かった．本研究はDPCデータを用いたわが国における初めての新生児DICについての大規模疫学研究報告である．新生児DICの発症は予後と強く関連し，より未熟な児ほど大きな影響を受ける．

キーワード：院内死亡率，在院日数，罹患率，新生児，DIC.

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