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ORIGINAL ARTICLE

Retrospective Study

Distinctive clinical features of spontaneous pneumoperitoneum in neonates: A retrospective analysis

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Abstract

BACKGROUND

Spontaneous pneumoperitoneum (SP) without gastrointestinal perforation rarely occurs in neonates, with most SP cases being idiopathic. Although SP usually follows a benign clinical course with favorable prognosis, it can become life-threatening in certain situations. In these cases, urgent surgical intervention may be required. Therefore, it may be difficult to decide when or how to perform prompt interventions.

AIM

To demonstrate the distinct clinical features of SP to guide appropriate management by comparing characteristics between SP and typical pneumoperitoneum secondary to gastrointestinal perforation.

METHODS

We retrospectively reviewed electronic medical records and identified 37 neonates with radiological evidence of pneumoperitoneum who were treated at our institution. Clinical variables were compared between neonates with SP without gastrointestinal perforation (Group A) and those with pneumoperitoneum secondary to gastrointestinal perforation (Group B). Clinical variables between groups were compared using Student's t-test and the chi-square test. The risk factors related to mortality were examined using multi-logistic regression analysis.

RESULTS

Group A comprised 35.1% (13/37) of the patients. The frequency of persistent pulmonary hypertension (53.8%) and pneumothorax (46.2%) before the

development of pneumoperitoneum was significantly higher in group A than in group B (P = 0.004). Platelet count and partial pressure of arterial oxygen (PaO2) were significantly lower in group A (P = 0.015 and 0.025, respectively). Overall mortality was significantly higher in group A than in group B (76.9% *vs* 16.7%, P = 0.001). Only preterm infants were significantly associated with high mortality (P = 0.041; odds ratio = 18.0). Accompaniment with persistent pulmonary hypertension and pneumothorax were also significantly high (P = 0.004) in group A, but these were not strongly associated with high mortality.

CONCLUSION

This study identified a higher mortality rate in patients with SP than that described in previous reports. Neonates with SP were more likely to have thrombocytopenia, pneumothorax, and persistent pulmonary hypertension. Prematurity was the most significant factor affecting mortality.

Key Words: Spontaneous pneumoperitoneum; Thrombocytopenia; Persistent pulmonary hypertension; Pneumothorax; Preterm

Core Tip: This study shows a higher mortality rate in a spontaneous pneumoperitoneum (SP) group than pneumoperitoneum secondary to gastrointestinal perforation, contrary to previous studies. Additionally, neonates with SP were more likely to have thrombocytopenia and accompany pneumothorax and persistent pulmonary hypertension. Preterm infants were the most significant factor affecting its mortality. These distinctive clinical features should be considered in the management of SP.

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INTRODUCTION

Pneumoperitoneum refers to the abnormal presence of intraperitoneal free air and is usually identified by radiography in extremely low-birth weight neonates with gastrointestinal perforation as most common cause[1-4]. Necrotizing enterocolitis and congenital anomalies causing intestinal perforation are common clinical findings[5,6]. Pneumoperitoneum generally requires emergent surgical intervention and may show variable clinical courses according to its etiology. However, spontaneous pneumoperitoneum (SP) not associated with gastrointestinal perforation rarely occurs in neonates[7,8]. Most cases of SP are idiopathic; however, SP may occur as a consequence of inadequate mechanical ventilation or massive cardiopulmonary resuscitation in critical neonates[9-11]. Although SP usually follows a benign clinical course with favorable prognosis, it can become life-threatening in certain situations. In these cases, urgent surgical intervention may be required. Therefore, it may be difficult to decide when or how to perform prompt interventions.

This study aimed to demonstrate the distinct clinical features of SP to guide appropriate management by comparing characteristics between SP and typical pneumoperitoneum secondary to gastrointestinal perforation.

MATERIALS AND METHODS

Subjects

We enrolled 37 neonates managed for pneumoperitoneum at our institution between January 2009 and December 2020. Pneumoperitoneum was diagnosed primarily based on radiological findings. Patients were divided into two groups: SP without gastrointestinal perforation (Group A) and pneumoperitoneum secondary to gastrointestinal perforation (Group B). This study was approved by the Institutional Review Board (IRB No. 05-2020-044) and was conducted in accordance with the recommendations of the IRB committee.

Analysis of clinical characteristics

Patients' electronic medical records were retrospectively reviewed to collect data regarding demographics, gestational data, clinical history before diagnosis (use of mechanical ventilation or high-frequency oscillation ventilation; history of persistent pulmonary hypertension, respiratory distress syndrome with bronchopulmonary dysplasia, pneumothorax, or cardiopulmonary resuscitation; and history of vasopressor infusion), laboratory parameters indicating inflammatory process (blood sugar level around diagnosis, C-reactive protein level, white blood cell count with segmented neutrophil count, platelet count), respiratory condition [pH, partial pressure of arterial oxygen (PaO2)], and treatment outcomes.

Statistical analysis

Clinical variables between groups were compared using Student's *t*-test and the chi-square test. The risk factors related to mortality in group A were examined using multi-logistic regression analysis (IBM SPSS Statistics v26, IBM Corp., Armonk, NY, United States). A P value of < 0.05 was considered statistically significant.

RESULTS

Demographic characteristics

Of the 37 patients, 13 (35.1%) had SP without gastrointestinal perforation (Group A), and 24 (64.9%) had pneumoperitoneum secondary to gastrointestinal perforation (Group B). Their demographic characteristics are presented in Table 1. There was a high proportion of male, preterm, and cesarean deliveries in both groups, but there were no significant differences between groups. Gestational age, birth weight, and 1- and 5-min Apgar scores were high in group B, while postnatal age at diagnosis was high in Group A. However, there were no significant differences (Table 1).

Preceding clinical characteristics before diagnosis

Persistent pulmonary hypertension (53.8%) and pneumothorax (46.2%) were significantly more common in group A (Figure 1A and B) than in group B (Figure 1C and D) ($P = 0.004$). There were no other significant differences in clinical characteristics between the groups, although patients in group A were more likely to have received mechanical ventilation at birth and of high-frequency oscillation ventilation and have a history of respiratory distress syndrome, cardiopulmonary resuscitation before diagnosis, and vasopressor infusion. Patients in group A also had a longer duration of mechanical ventilation compared with group B (Table 2).

Comparison of several laboratory parameters at diagnosis and outcomes

Blood sugar levels were higher in group A than in group B without significancy. By contrast, C-reactive protein level, white blood cell count, and neutrophil count were higher in group B, but the difference was not significant. Platelet count, pH, and PaO2 were lower in group A than in group B, and the differences in platelet count and PaO2 were significant lower in group A ($P = 0.015$ and 0.025, respectively). Overall mortality was significantly higher in group A than in group B (76.9% *vs* 16.6%, $P = 0.001$) (Table 3).

Characteristics of SP without gastrointestinal perforation

Five patients with SP were managed by non-operative treatment, and 8 patients underwent surgery due to the presence of abdominal rigidity and clinical deterioration during non-surgical management. Surgical exploration did not reveal any obvious underlying conditions. The overall mortality rate among patients with SP was 76.9%. Mortality rate was higher in preterm infants, those treated by non-operative management, and in cases accompanied by pneumothorax, persistent pulmonary hypertension, respiratory distress syndrome, vasopressor infusion, cardiopulmonary resuscitation, thrombocytopenia, and application of high-frequency oscillation ventilation system. Only preterm infants were significantly associated with high mortality ($P = 0.041$; odds ratio = 18.0) (Table 4).

Characteristics of pneumoperitoneum with gastrointestinal perforation

Among neonates with pneumoperitoneum with gastrointestinal perforation, there were 7 and 7 cases of gastric perforation and necrotizing enterocolitis, respectively, 2 cases of single intestinal perforation, 4 cases of Hirschsprung's disease, 2 cases of esophageal atresia with distal tracheoesophageal fistula, and 1 case of intestinal atresia. The mortality rate was 16.6% (Table 5).

Table 1 Demographic findings

Variables	Group A, *n* = 13	Group B, *n* = 24	*P* value
Sex (male/female)	12/1	17/7	0.224
GA, wk	29.5 ± 5.3 (23-39)	31.7 ± 5.2 (23-39)	0.216
Preterm/full term	10/3 (76.9%)	16/8 (66.7%)	0.515
Birth weight, g	1479.2 ± 1071.2 (450-3670)	1888.2 ± 986.5 (670-3450)	0.189
Delivery (NSVD/CS)	1/12	10/14	0.057
Postnatal age at diagnosis, d	18.8 ± 29.9 (0-111)	12.1 ± 18.5 (1~ 79)	0.499
Apgar at 1 min	4.0 ± 2.5 (0-8)	4.3 ± 1.5 (0-8)	0.936
Apgar at 5 min	5.8 ± 2.0 (1-9)	6.5 ± 1.5 (0-9)	0.825

Values are presented as mean ± standard deviation or patient number. GA: Gestational age; NSVD: Normal spontaneous vaginal delivery; CS: Cesarean section.

Table 2 Preceding clinical history before diagnosing a pneumoperitoneum

Variables	Group A, *n* = 13	Group B, *n* = 24	*P* value	Odds ratio, 95%CI
MV at birth (yes/no)	12/1	17/7	0.216	4.333
HFOV (yes/no)	5/13	3/24	0.100	4.375
PPHN (yes/no)	7/6	2/22	0.004	12.833
RDS (yes/no)	11/2	15/9	0.262	3.3
Pneumothorax (yes/no)	6/7	1/23	0.004	19.7
CPR (yes/no)	3/10	2/22	0.321	3.3
Vasopressor infusion (yes/no)	11/2	12/12	0.074	5.5
MV duration, d	17.1 ± 30.2 (1-111)	12.4 ± 21.7 (2-79)	0.067	-

Values are presented as patient number or mean ± standard deviation. CI: Confidence intervals; MV: Mechanical ventilation; HFOV: High-frequency oscillation ventilation; PPHN: Persistent pulmonary hypertension; RDS: Respiratory distress syndrome; CPR: Cardiopulmonary resuscitation.

DISCUSSION

Gastrointestinal perforation is the most common cause of pneumoperitoneum and requires prompt surgical exploration[1-4]. In neonates, these cases present a clinical challenge for neonatologists and pediatric surgeons. Meanwhile, SP not associated with gastrointestinal perforation during the neonatal period has been described sporadically[12-15]. The clinical course of SP is variable; some patients are asymptomatic and do not require surgical intervention, while others can become critically unwell. Further, there are some controversial issues in diagnosis and management due to the lack of a clear etiology. A few previous reports described SP as a benign pneumoperitoneum because it generally presents with asymptomatic intraperitoneal air without signs or symptoms of peritonitis and suggested careful management to avoid unnecessary surgery if possible[7,8,15,16]. There are not many reports about its prevalence and consensus regarding the optimal treatment protocol, but it is estimated to contribute to 5.4%-7.8% of all cases of neonatal pneumoperitoneum and the laparotomy rate for this condition is known to be as high as 28%[6,17]. This study revealed an unexpectedly high prevalence of SP, which contributed to approximately one-third of all pneumoperitoneum cases. Generally, pneumoperitoneum is more likely to occur in extremely low birth weight neonates due to necrotizing enterocolitis. However, we found no significant differences in gestational age and birth weight between neonates with SP and those with pneumoperitoneum with gastrointestinal perforation, although those with SP showed low gestational age and lower birth weight. Therefore, it is important to differentiate SP from cases of pneumoperitoneum associated with gastrointestinal perforation to ensure appropriate management.

Several possible origins of free air in cases of SP were presumed: Intrathoracic, gynecologic, intra-abdominal, iatrogenic, and miscellaneous[2,18,19]. Among those, there were some suggested clinical factors with including inadequate mechanical ventilation, a massive cardiopulmonary resuscitation, air

Table 3 Laboratory findings at diagnosis and outcomes

Variables	Group A, *n* = 13	Group B, *n* = 24	*P* value
Blood sugar, mg%	152.1 ± 58.2 (69-235)	148.3 ± 51.4 (85-294)	0.790
CRP, IU/L	1.28 ± 1.60 (0.01-4.88)	2.24 ± 4.03 (0.03-17.94)	0.649
WBC, 10^3/μL	14641.5 ± 7008.6 (3810-25470)	14568.8 ± 9349.4 (4410-37360)	0.561
Segmented neutrophil, %	57.5 ± 17.4 (20.3-87.0)	62.1 ± 12.8 (34.1-81.4)	0.479
PLT, 10^3/μL	156.1 ± 115.9 (6.0-371.0)	272.9 ± 143.8 (83.0-565.0)	0.015
Thrombocytopenia	8 / 13	5 / 24	0.013
pH	7.26 ± 0.15 (6.95-7.43)	7.27 ± 0.17 (6.92-7.48)	0.696
PaO2, mmHg	55.4 ± 19.2 (18.0-86.8)	100.9 ± 58.3 (46.3-227.2)	0.025
Overall mortality, %	76.9 (10/13)	16.6 (4/24)	0.001

Values are presented as mean ± standard deviation or patient number. CRP: C-reactive protein; WBC: White blood cell; PLT: Platelet.

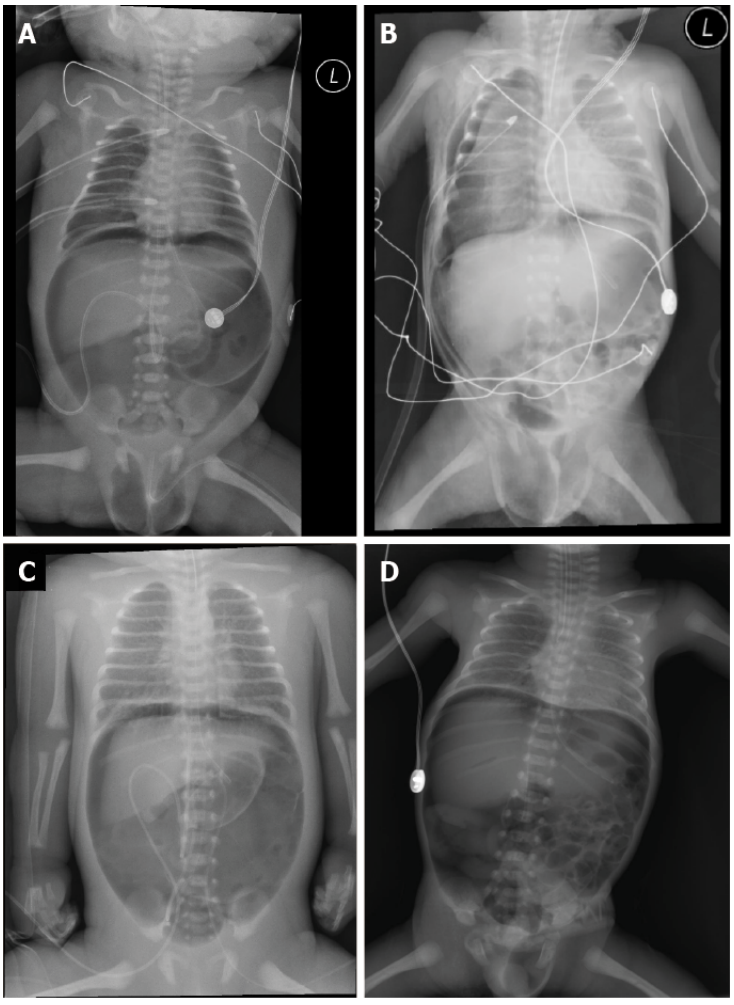

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Figure 1 Radiologic findings of pneumoperitoneum. A and B: Spontaneous pneumoperitoneum without gastrointestinal perforation accompanying pneumothorax; C and D: Pneumoperitoneum secondary to gastrointestinal perforation without pneumothorax.

leak syndrome, and other pulmonary conditions associated with prematurity[9,10,20]. Of these, pneumothorax is a frequent preceding sign and has been demonstrated to show a favorable clinical course in most of the reported cases[2,7,8]. There was also a relatively high proportion of prematurity regardless of gastrointestinal perforation in this study, but the mortality rate was significantly higher in SP cases than in cases associated with gastrointestinal perforation (76.9% *vs* 16.7%, P = 0.001). Even

Table 4 Clinical characteristics and analysis of factor affecting mortality in group A, *n* = 13

Variables	No of cases (%)	*P* value	Odd ratio (95%CI)
Management			
Non-operative	5 (38.5)		
Operation	8 (61.5)		
Mortality, overall	10/13 (76.9)		
Mortality in			
Non-operative	5/5 (100)		
Operative	5/8 (62.5)	0.231	0.625 (0.365-1.069)
Pneumothorax (+)	6/6 (100)		
Pneumothorax (-)	4/7 (57.1)	0.067	1.750 (0.921-3.324)
PPHN (+)	6/7 (85.7)		
PPHN (-)	4/6 (66.7)	0.416	3.0 (0.199-45.244)
RDS (+)	9/11 (81.8)		
RDS (-)	1/2 (50.0)	0.326	4.5 (0.190-106.8)
HFOV (+)	4/5 (80.0)		
HFOV (-)	6/8 (75.0)	0.912	1.333 (0.088-20.108)
Vasopressor (+)	9/11 (81.8)		
Vasopressor (-)	1/2 (50.0)	0.326	4.5 (0.190-106.823)
CPR (+)	3/3 (100)		
CPR (-)	7/10 (70.0)	0.279	1.429 (0.952-2.143)
Thrombocytopenia (+)	7/8 (87.5)		
Thrombocytopenia (-)	3/5 (60.0)	0.51	4.667 (0.197-73.384)
Full-term	1/3 (33.3)		
Preterm	9/10 (90.0)	0.041	18.0 (0.758-427.291)

PPHN: Persistent pulmonary hypertension; RDS: Respiratory distress syndrome; CPR: Cardiopulmonary resuscitation.

though surgical exploration was performed in some cases with abdominal rigidity or clinical deterioration despite conservative management, no obvious cause for SP was identified in any of our patients. In contrast, we found several well-known causes of gastrointestinal perforation in this study.

There were no significant differences in demographic findings and laboratory results at the time of diagnosis, including white blood cell count, segmented neutrophil proportion, and C-reactive protein level, implying an inflammatory process regardless of gastrointestinal perforation. Therefore, it is difficult to predict the characteristics of pneumoperitoneum based on only typical clinical presentations, such as abdominal distention and radiologic finding. Regarding clinical conditions before the occurrence of pneumoperitoneum, there were important differences between groups. Of note, some respiratory problems (persistent pulmonary hypertension, pneumothorax, and respiratory distress syndrome) and consequent supportive management (application of mechanical ventilation and its duration, high-frequency oscillation ventilation, vasopressor infusion, and cardiopulmonary resuscitation) were relatively common in the SP group. These findings may also be considered as possible causes described in previous reports[10,11,15,16,21], but more studies are needed to reach a suitable conclusion. This study showed a significantly high proportion of pneumothorax and persistent pulmonary hypertension in the SP group ($P = 0.004$), but these were not significantly associated with the risk of pneumoperitoneum. Instead, patients with SP had a significantly decreased platelet count (thrombocytopenia) and PaO2 compared with those in the pneumoperitoneum secondary to gastrointestinal perforation group. Additionally, a significantly high mortality rate (76.9%) in the SP group was an interesting finding. It is likely that the above laboratory findings could affect morbidity and mortality. These critical factors should be considered, as they may influence the progress and management of SP cases.

Table 5 Clinical characteristics of Group B, *n* = 24

Variable	Cases, *n* (%)
Associated gastrointestinal conditions	
Gastric perforation	7 (29.2)
NEC	7 (29.2)
SIP	2 (8.3)
HD	4 (16.6)
Intestinal atresia	1 (4.2)
EA /c TEF	2 (8.3)
Malrotation	1 (4.2)
Mortality, overall	4 (16.6)

NEC: Necrotizing enterocolitis; SIP: Single intestinal perforation; HD: Hirschsprung disease; EA /c TEF: Esophageal atresia with distal tracheoesophageal fistula.

The management of patients with SP depends on their condition, but deciding between non-operative or operative management presents a treatment dilemma for clinicians. Typical clinical and laboratory findings are not sufficient to support such a decision. In our study, there were no significant differences in types of management (surgical or non-surgical). Surgical management was performed in 53.8% of SP cases when clinical examination revealed abdominal rigidity and clinical deterioration suggestive of perforation during conservative care. The rate of surgical management of SP in our study was higher than that cited by previous reports[6,17]. During conservative management, surgical procedure was performed due to unusual and not improved clinical situations. However, a previous case reported good outcomes in a patient with idiopathic SP after a period of observation, suggesting that surgical intervention should only be performed in necessary cases to avoid unnecessary procedures[4,7,8,15,16,21]. On the contrary, this study revealed a relatively high mortality rate in patients who did not undergo surgery (100% *vs* 62.5%). In this study, we could not reveal clear factors related to its high mortality. Nevertheless, it is presumed to be caused by combination of some clinical situations. Of note, more than two-thirds of cases with SP were preterm infants with a mean gestational age of 29.5 wk. Therefore, the high mortality rate may be related to underlying pulmonary conditions, especially persistent pulmonary hypertension and pneumothorax, and other critical situations requiring vasopressor infusion and cardiopulmonary resuscitation. However, this study did not find a significant correlation between these variables with high mortality. Instead, only preterm infants were significantly associated with high mortality (P = 0.041; odds ratio = 18.0, 95% confidence interval 0.758-427.29).

Compared to a pneumoperitoneum secondary to gastrointestinal perforation, SP showed some specific clinical features; (1) A high association with proceeding clinical condition, persisted pulmonary hypertension and pneumothorax; (2) Frequently accompanied with a thrombocytopenia and lower partial pressure of arterial oxygen; and (3) A high mortality, especially in preterm neonates.

This study had a few limitations. First, this was a retrospective study conducted at a single institution and all diagnoses were based solely on radiologic findings; therefore, we cannot exclude the possibility of selection bias. Second, the sample size was small, which may limit the interpretation of the results. Considering the rarity of SP, further studies with larger sample sizes are warranted to improve our understanding of this condition. Finally, the results are limited by the lack of a comparative study for this clinical situation with inclusion of a control group without pneumoperitoneum. Nevertheless, this study is valuable as it furthers our understanding of the distinctive features of SP.

CONCLUSION

SP is associated with a higher mortality rate than pneumoperitoneum secondary to gastrointestinal perforation, and this rate was higher than that reported by previous studies. Additionally, neonates with SP were more likely to have thrombocytopenia and accompany pneumothorax and persistent pulmonary hypertension. Preterm infants were the most significant factor affecting its mortality. These distinctive clinical features should be considered in the management of SP. Further studies with larger sample sizes are warranted to validate these results.

ARTICLE HIGHLIGHTS

Research background

Spontaneous pneumoperitoneum (SP) without gastrointestinal perforation rarely occurs in neonates, with most cases being idiopathic. Although it usually follows a benign clinical course with favorable prognosis, it can become life-threatening in certain situations.

Research motivation

SP is associated with a higher mortality rate than pneumoperitoneum secondary to gastrointestinal perforation, and this rate was higher than that reported by previous studies.

Research objectives

To demonstrate the distinct clinical features of SP to guide appropriate management by comparing characteristics between SP and typical pneumoperitoneum secondary to gastrointestinal perforation.

Research methods

Retrospectively reviewed electronic medical records and identified 37 neonates with radiological evidence of pneumoperitoneum who were treated at our institution. Clinical variables were compared between neonates with SP without gastrointestinal perforation (Group A) and those with pneumoperitoneum secondary to gastrointestinal perforation (Group B).

Research results

Compared to a pneumoperitoneum secondary to gastrointestinal perforation, SP showed some specific clinical features: (1) A high association with proceeding clinical condition, persisted pulmonary hypertension and pneumothorax; (2) Frequently accompanied with a thrombocytopenia and lower partial pressure of arterial oxygen; and (3) A high mortality, especially in preterm neonates.

Research conclusions

This study identified a higher mortality rate in patients with SP than that described in previous reports. Neonates with SP were more likely to have thrombocytopenia, pneumothorax, and persistent pulmonary hypertension. Prematurity was the most significant factor affecting mortality.

Research perspectives

There were a few limitations: First, this was a retrospective study conducted at a single institution and all diagnoses were based solely on radiologic findings; second, the sample size was small which may limit the interpretation of the results; third, the results are limited by the lack of a comparative study for this clinical situation with inclusion of a control group without pneumoperitoneum. Nevertheless, this study is valuable as it furthers our understanding of the distinctive features of SP.

FOOTNOTES

Author contributions: Cho YH and Kim SH contributed to study conception and design, drafting and revision of the manuscript, and finalization of the submission; Kim HY contributed to data analysis and interpretation; All authors reviewed the final manuscript.

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Institutional review board statement: This study was reviewed and approved by the Pusan National University Yangsan Hospital Institutional Review Board also approved to progress this project without informed consent, No. 05-2020-044.

Informed consent statement: This study is a retrospective cohort study. Therefore, it was impossible to get consent from patients and their guardians in advance. This study was not for research purpose about human subject itself, so it does not contain any concerned data. It may be published as a journal worthy of being open in public after collecting data of managements for the past 12 years. Moreover, Pusan National University Yangsan Hospital Institutional Review Board also approved to carry out this project without informed consent

Conflict-of-interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data sharing statement: No additional data are available. All data relevant to the study are included in the article and are also available upon reasonable request.

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