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Occurrence and Time of Onset of Intraventricular Hemorrhage in Preterm Neonates

A Systematic Review and Meta-Analysis of Individual Patient Data

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IMPORTANCE Intraventricular hemorrhage (IVH) has been described to typically occur during the early hours of life (HOL); however, the exact time of onset is still unknown.

OBJECTIVE To investigate the temporal distribution of IVH reported in very preterm neonates.

DATA SOURCES PubMed, Embase, Cochrane Library, and Web of Science were searched on May 9, 2024.

STUDY SELECTION Articles were selected in which at least 2 cranial ultrasonographic examinations were performed in the first week of life to diagnose IVH. Studies with only outborn preterm neonates were excluded.

DATA EXTRACTION AND SYNTHESIS Data were extracted independently by 3 reviewers. A random-effects model was applied. This study is reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline. The Quality in Prognostic Studies 2 tool was used to assess the risk of bias.

MAIN OUTCOMES AND MEASURES The overall occurrence of any grade IVH and severe IVH among preterm infants was calculated along with a 95% CI. The temporal distribution of the onset of IVH was analyzed by pooling the time windows 0 to 6, 0 to 12, 0 to 24, 0 to 48, and 0 to 72 HOL. A subgroup analysis was conducted using studies published before and after 2007 to allow comparison with the results of a previous meta-analysis.

RESULTS A total of 21 567 records were identified, of which 64 studies and data from 9633 preterm infants were eligible. The overall rate of IVH did not decrease significantly before vs after 2007 (36%; 95% CI, 30%-42% vs 31%; 95% CI, 25%-36%), nor did severe IVH (10%; 95% CI, 7%-13% vs 11%; 95% CI, 8%-14%). The proportion of very early IVH (up to 6 HOL) after 2007 was 9% (95% CI, 3%-23%), which was 4 times lower than before 2007 (35%; 95% CI, 24%-48%). IVH up to 24 HOL before and after 2007 was 44% (95% CI, 31%-58%) and 25% (95% CI, 15%-39%) and up to 48 HOL was 82% (95% CI, 65%-92%) and 50% (95% CI, 34%-66%), respectively.

CONCLUSION AND RELEVANCE This systematic review and meta-analysis found that the overall prevalence of IVH in preterm infants has not changed significantly since 2007, but studies after 2007 showed a later onset as compared with earlier studies, with only a small proportion of IVHs occurring before 6 HOL.

Supplemental content

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Preterm birth is one of the most challenging health problems, associated with high mortality and long-term disability. Intraventricular hemorrhage (IVH) is a common and the most significant early complication responsible for adverse outcomes in very preterm infants. Extreme alterations in perinatal hemodynamics, cerebral blood flow and oxygenation, as well as infections and proinflammatory states are associated with underlying mechanisms that contribute to the development of IVH.[1-6] A 2022 meta-analysis by Lai et al[7] found that the incidence of any IVH was 34.3%, whereas the incidence of severe IVH was 15.0% for infants with gestational age (GA) less than 28 weeks. Improvements in neonatal care may reduce the risk of both mortality and IVH. However, a reduction in mortality of extremely preterm infants at the highest risk of IVH may offset the expected decrease in IVH by an increase in the number of survivors of IVH.[2,3] These 2 trends together may lead to a stable overall rate of IVH.[8]

As IVH is multifactorial, theoretically, the use of measures from a care bundle during different (antepartum, intrapartum, and postpartum) time windows has the greatest potential to reduce IVH. When the effectiveness of these interventions is assessed, it is essential to know when IVH occurs. Most IVH occurs during the first 3 days of life[9]; however, the exact onset is typically unknown in individual events.[10] A 2014 meta-analysis found that 48% of all IVH events occurred during the first 0 to 6 hours of life (HOL) and 38% occurred after 24 HOL in neonates weighing 1500 g or less.[11]

Neuroimaging, particularly cranial ultrasonography, is the primary diagnostic tool for the detection of IVH. Repeated IVH screening at predetermined times using cranial ultrasonography provides an opportunity to detect the approximate time of onset of bleeding.[12] Infrequent imaging may fail to capture the precise moment when IVH occurs, making it difficult to establish a cause-and-effect relationship between IVH and known risk factors.[13-15] Furthermore, screening protocols for cranial ultrasonography show considerable heterogeneity among neonatal intensive care units.

The primary aim of our study was to explore the temporal distribution of the onset of IVH in preterm infants by a systematic review and meta-analysis of previous studies reporting IVH. The secondary aim was to test hypotheses that recent improvements in neonatal care were associated with a reduction in the prevalence of IVH and/or delayed onset of IVH. As there was no single therapeutic breakthrough innovation in neonatal medicine in recent years that would have provided a clearly identifiable time boundary, 2007 was used as the cutoff date for the time analysis. This also allowed comparison with a previous meta-analysis.[11]

Key Points

Question What are the occurrence and temporal distribution of intraventricular hemorrhage (IVH) in very preterm neonates during the first week of life?

Findings This systematic review and meta-analysis including 64 studies and 9633 preterm neonates found that the overall prevalence of IVH in preterm neonates has not changed significantly over the past 20 to 40 years. However, IVH earlier than 6 hours of life has been reduced to less than 10% of all IVH events.

Meaning These data suggest that although preventive measures have been implemented, IVH has occurred later but its prevalence has not been reduced.

Methods

This systematic review and meta-analysis is reported following Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline,[16] the Cochrane Handbook,[17] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[18] The protocol was registered in PROSPERO (identifier CRD42022370884).[19]

Eligibility Criteria

Cohort studies, case series, and clinical trial or conference abstracts were eligible; case reports and studies with only outborn preterm neonates were excluded from our systematic review. Our primary aim was to describe the occurrence and temporal distribution of the onset of IVH in preterm neonates (birth weight ≤1500 g and GA ≤32 weeks) during the first week of life. Studies in which cranial ultrasonography was performed at least twice during the first week of life to diagnose IVH were selected.

Information Sources and Search Strategy

PubMed, Embase, Cochrane Library, and Web of Science were searched on May 9, 2024. Reference lists of eligible studies and review articles were also screened via citation chaser.[20] No restrictions were applied. The search key included age, the disease in question (IVH), and a screening domain (eTable 1 in Supplement 1).

Screening and Selection

After removing duplicates using reference management software (EndNote X9; Clarivate Analytics), Zs. N. and G. M. independently screened titles, abstracts, and full texts against predefined eligibility criteria. Cohen κ was used to assess interrater agreements during the selection process. A third author (M. Sz.) resolved any conflicts.

Data Extraction

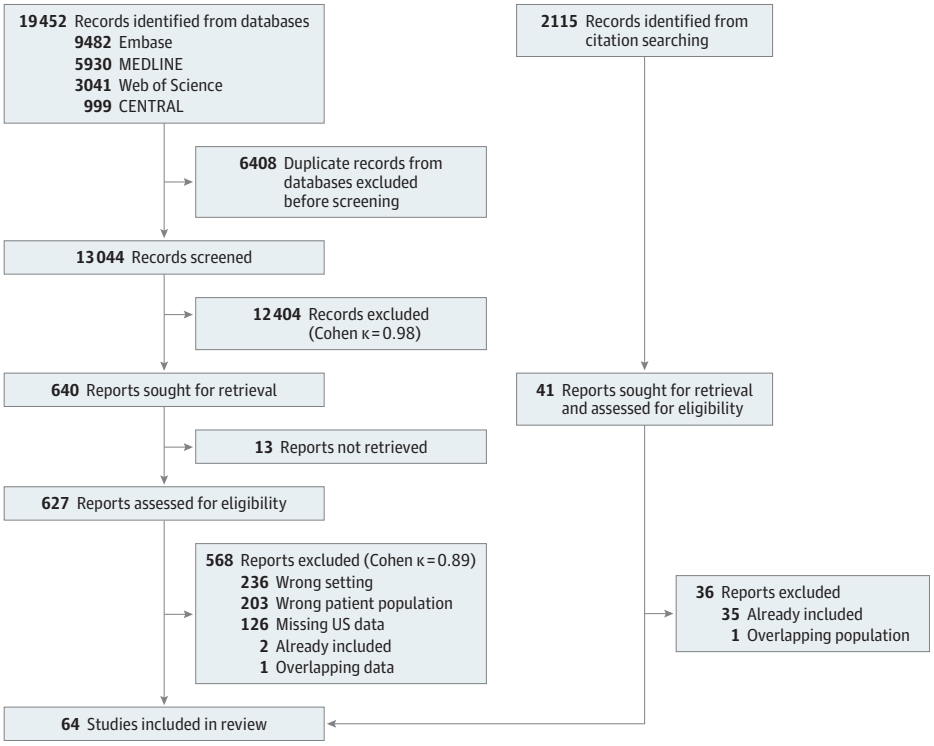
Three independent authors (Zs. N., G. M., and E. Sz.) extracted data from eligible studies into an Excel spreadsheet (Office 365; Microsoft). A fourth independent author (M. Sz.) resolved all disagreements. The following data were extracted from each eligible article or conference abstract: study name, first author, countries, publication year, study period, design and methods, total number of patients with any grade and with severe IVH, gestational age, birth weight, the onset of IVH, outborn status, antenatal steroid rate, and early and total mortality.

Risk of Bias Assessment

The Quality in Prognostic Studies 2 (QUIPS-2) tool[21] was used by 2 independent authors (Zs. N. and G. M.). Any disagreements were resolved by a third investigator (M. V.).

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Figure 1. Flowchart of the Screening and Selection Process of the Studies



Statistical Analysis

Statistical analyses were performed according to Harrer et al.[22] All analyses were conducted using a random-effects model. The distribution of IVH onset time was analyzed by pooling the time windows 0 to 6, 0 to 12, 0 to 24, 0 to 48, and 0 to 72 HOL. A random intercept logistic regression approach was used to analyze the overall proportions of IVH and severe IVH.[23] Results and pooled proportions with 95% CIs were visualized in forest plots. Prediction intervals were also calculated. A subgroup analysis was conducted using studies published before and after 2007 to allow comparison with the results of a previous meta-analyses.[11] Heterogeneity was assessed using Higgins and Thompson I^2 statistics. Statistical analyses were performed using R software version 4.1.2 (R Project for Statistical Computing) except for the interval-censored survival analysis, which was performed using SAS software. A detailed statistical description can be found in the eMethods in Supplement 1.

Results

Search and Selection

In total, 19 452 and 2115 records were identified by systematic search and citation chasing, respectively. Sixty-four studies[12,24-83] were included in the quantitative analysis, 2 of which were included only in the calculation of the proportion of severe IVH occurrence among preterm neonates (**Figure 1**). All reasonable attempts were made to contact the authors for additional data. On the basis of their responses, data for more than 2000 individual patients from 14 articles[12,56,59,61-63,65,70,73-75,78,79] were included to provide a more accurate estimate of the temporal distribution of IVH onset.

Characteristics of Studies Included

In total, 9633 infants were included, mainly from Europe and North America. Most of the studies presented and analyzed were cohort studies (retrospective: 12 studies[25,29,57,58,64,71,76-78,81,83,84] and prospective: 40 studies[12, 24, 26-28, 32-34, 36-40, 42, 44-48, 51, 52, 54-56, 59-62, 65-68, 70, 72, 74, 75, 79, 80, 82, 85]). Severe IVH events were reported in 51 studies[12,24-29,31,33-40,42,44-49,52-57,59,61,63-65,68-82,85,86] Baseline characteristics of the studies included are detailed in eTable 2 in Supplement 1.

Proportions of Any Grade and Severe IVH

Data from 61 included studies[12,24-86] of 9218 infants were used to calculate the overall occurrence of IVH among preterm neonates. Most of the articles selected for the before 2007 subgroup had been included in the previous meta-analysis.[11]

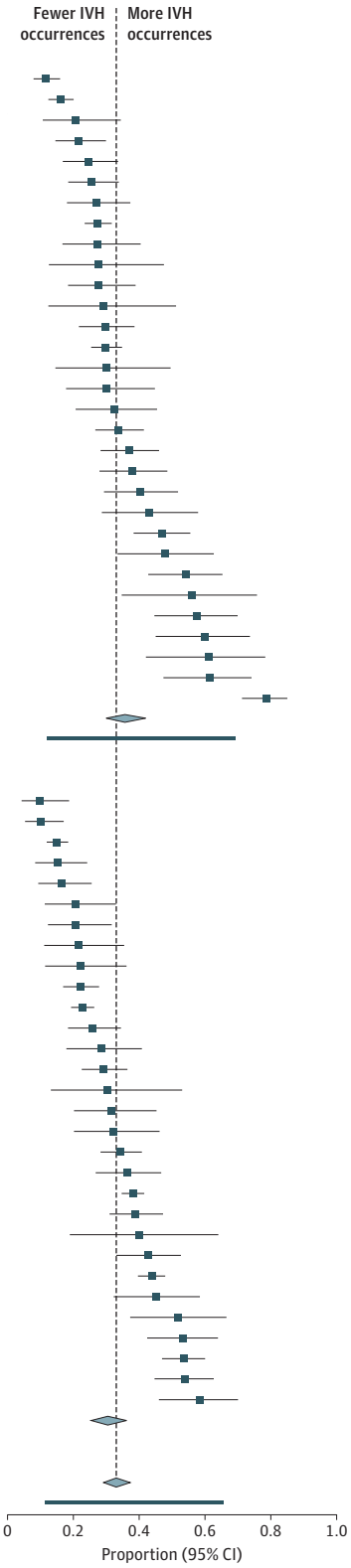
The overall occurrence of IVH in preterm infants was 33% (95% CI, 29%-37%), whereas for severe IVH, it was 10% (95% CI, 8%-13%). Neither the total occurrence of IVH (36% [95% CI, 30%-42%] vs 31% [95% CI, 25%-36%]; P = .19) nor the occurrence of severe IVH (10% [95% CI, 7%-13%] vs 11% [95% CI, 8%-14%]; P = .67) was different in subgroups before vs after 2007 (**Figure 2** and **Figure 3**).

In the subgroups of gestational age, the studies before 2007 reported IVH occurrence of 33% (95% CI, 26%-41%) in infants with GA less than 28 weeks, 32% (95% CI, 22%-44%) in infants with GA less than 32 weeks, and 38% (95% CI,

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Figure 2. Overall Intraventricular Hemorrhage (IVH) Occurrence in Preterm Infants Before and After 2007

Source	No. Events	No. Total	Proportion (95% CI)
Before 2007			
Zanardo et al,[24] 2008	33	287	0.11 (0.08-0.16)
Salafia et al,[25] 1995	65	406	0.16 (0.13-0.20)
Florio et al,[26] 2006	11	53	0.21 (0.11-0.34)
Kluckow and Evans,[27] 2000	27	126	0.21 (0.15-0.30)
Krediet et al,[28] 2006	28	114	0.25 (0.17-0.34)
Evans and Kluckow,[29] 1996	36	141	0.26 (0.19-0.34)
Paradisis et al,[30] 2009	25	93	0.27 (0.18-0.37)
Ment et al,[31] 1995	138	504	0.27 (0.24-0.31)
Sarkar et al,[32] 2005	17	62	0.27 (0.17-0.40)
Paradisis et al,[33] 2006	8	29	0.28 (0.13-0.47)
van Bel et al,[34] 2002	23	83	0.28 (0.18-0.39)
Meek et al,[35] 1999	7	24	0.29 (0.13-0.51)
Osborn et al,[36] 2003	38	128	0.30 (0.22-0.38)
Perlman and Volpe,[37] 1986	126	421	0.30 (0.26-0.35)
Chalak et al,[38] 2011	9	30	0.30 (0.15-0.49)
Amato et al,[39] 1989	15	50	0.30 (0.18-0.45)
Dolfin et al,[40] 1983	20	62	0.32 (0.21-0.45)
Dani et al,[41] 2005	59	175	0.34 (0.27-0.41)
Babnik et al,[42] 2006	46	125	0.37 (0.28-0.46)
Thorburn et al,[43] 1982	36	95	0.38 (0.28-0.48)
Weindling et al,[44] 1985	33	82	0.40 (0.30-0.52)
Rumack et al,[45] 1985	21	49	0.43 (0.29-0.58)
Bada et al,[46] 1989	68	145	0.47 (0.39-0.55)
McDonald et al,[47] 1984	24	50	0.48 (0.34-0.63)
Yang et al,[48] 1990	45	83	0.54 (0.43-0.65)
Iyer et al,[49] 2015	14	25	0.56 (0.35-0.76)
Ment et al,[50] 1985	38	66	0.58 (0.45-0.70)
Szymonowicz and Yu et al,[51] 1984	30	50	0.60 (0.45-0.74)
Ment et al,[52] 1984	19	31	0.61 (0.42-0.78)
Perlman et al,[53] 1983	35	57	0.61 (0.48-0.74)
Bada et al,[54] 1984	122	155	0.79 (0.71-0.85)
Random-effects model		3801	0.36 (0.30-0.42)
Prediction interval			(0.12-0.69)
Heterogeneity: I^2 = 91% (89%-93%); P < .001			
After 2007			
Ikeda et al,[55] 2015	8	81	0.10 (0.04-0.19)
Katheria et al,[56] 2018	13	127	0.10 (0.06-0.17)
Schreiner et al,[57] 2021	80	536	0.15 (0.12-0.18)
Kalani et al,[58] 2016	14	93	0.15 (0.08-0.24)
Ishiguro et al,[59] 2014	15	92	0.16 (0.09-0.25)
Tanaka et al,[60] 2024	13	63	0.21 (0.11-0.33)
Martini et al,[61] 2022	16	77	0.21 (0.12-0.32)
Popat et al,[62] 2019	11	51	0.22 (0.11-0.35)
Galderisi et al,[63] 2019	11	50	0.22 (0.12-0.36)
Duppré et al,[64] 2015	55	250	0.22 (0.17-0.28)
Alderliesten et al,[65] 2013	148	652	0.23 (0.20-0.26)
Thanhaeuser et al,[66] 2018	33	128	0.26 (0.18-0.34)
Najib et al,[67] 2019	19	67	0.28 (0.18-0.41)
Vesoulis et al,[12] 2021	54	185	0.29 (0.23-0.36)
Noori et al,[68] 2014	7	23	0.30 (0.13-0.53)
Katheria et al,[69] 2014	19	60	0.32 (0.20-0.45)
da Costa et al,[70] 2018	18	56	0.32 (0.20-0.46)
Xing et al,[71] 2022	82	239	0.34 (0.28-0.41)
June et al,[72] 2023	36	99	0.36 (0.27-0.47)
Juul et al,[73] 2020	344	903	0.38 (0.35-0.41)
Vesoulis et al,[74] 2020	61	157	0.39 (0.31-0.47)
Cimatti et al,[75] 2020	8	20	0.40 (0.19-0.64)
Bates et al,[76] 2016	46	108	0.43 (0.33-0.52)
Zanelli et al,[77] 2023	279	638	0.44 (0.40-0.48)
El-Dib et al,[78] 2022	28	62	0.45 (0.32-0.58)
Deshpande et al,[79] 2020	26	50	0.52 (0.37-0.66)
Jiang et al,[80] 2023	49	92	0.53 (0.43-0.64)
Lampe et al,[81] 2020	136	254	0.54 (0.47-0.60)
Farag et al,[82] 2022	71	132	0.54 (0.45-0.62)
Espiritu Rojas et al,[83] 2021	42	72	0.58 (0.46-0.70)
Random-effects model		5417	0.31 (0.25-0.36)
Prediction interval			(0.10-0.63)
Heterogeneity: I^2 = 92% (90%-94%); P < .001			
Random-effects model		9218	
Prediction interval			0.33 (0.29-0.37)
Heterogeneity: I^2 = 92% (90%-93%); P < .001			(0.11-0.66)
Test for subgroup differences: χ^2_1 = 1.73; P = .19			

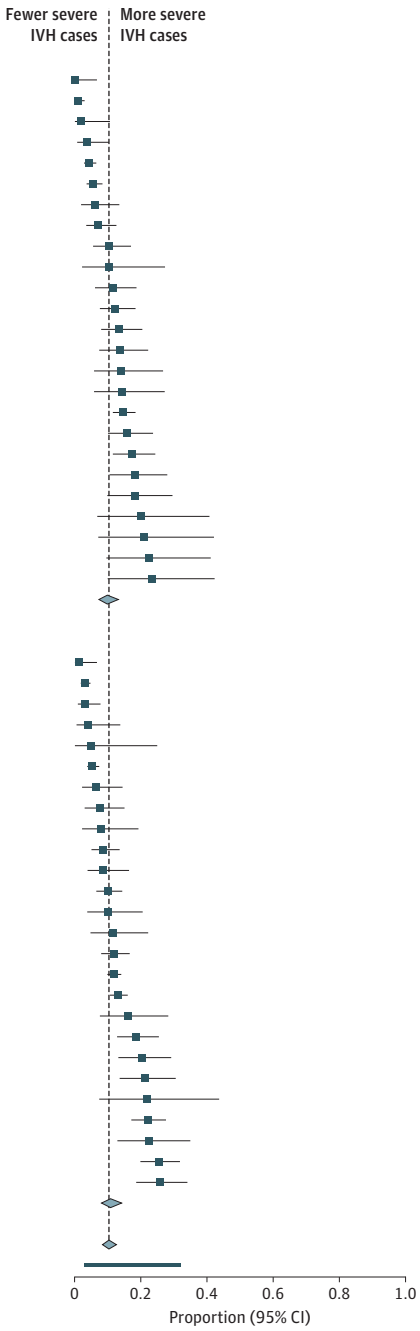


Diamonds indicate overall proportions.

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Figure 3. Overall Severe Intraventricular Hemorrhage (IVH) Occurrence in Preterm Infants Before and After 2007

Source	No. Events	No. Total	Proportion (95% CI)
Before 2007			
Florio et al,[26] 2006	0	53	0.00 (0.00-0.07)
Zanardo et al,[24] 2008	3	287	0.01 (0.00-0.03)
Amato et al,[39] 1989	1	50	0.02 (0.00-0.11)
Weindling et al,[44] 1985	3	82	0.04 (0.01-0.10)
Ment et al,[31] 1995	22	505	0.04 (0.03-0.07)
Salafia et al,[25] 1995	23	406	0.06 (0.04-0.08)
van Bel et al,[34] 2002	5	83	0.06 (0.02-0.14)
Evans and Kluckow,[29] 1996	10	141	0.07 (0.03-0.13)
Kluckow and Evans,[27] 2000	13	126	0.10 (0.06-0.17)
Paradisis et al,[33] 2006	3	29	0.10 (0.02-0.27)
Krediet et al,[28] 2006	13	114	0.11 (0.06-0.19)
Bada et al,[54] 1984	19	155	0.12 (0.08-0.18)
Osborn et al,[36] 2003	17	128	0.13 (0.08-0.20)
Thorburn et al,[53] 1982	13	95	0.14 (0.07-0.22)
McDonald et al,[47] 1984	7	50	0.14 (0.06-0.27)
Rumack et al,[45] 1985	7	49	0.14 (0.06-0.27)
Perlman and Volpe,[37] 1986	62	421	0.15 (0.11-0.18)
Babnik et al,[42] 2006	20	125	0.16 (0.10-0.24)
Bada et al,[46] 1989	25	145	0.17 (0.11-0.24)
Yang et al,[48] 1990	15	83	0.18 (0.10-0.28)
Dolfin et al,[40] 1983	12	66	0.18 (0.10-0.30)
Iyer et al,[49] 2015	5	25	0.20 (0.07-0.41)
Meek et al,[35] 1999	5	24	0.21 (0.07-0.42)
Ment et al,[52] 1984	7	31	0.23 (0.10-0.41)
Chalak et al,[38] 2011	7	30	0.23 (0.10-0.42)
Random-effects model		3303	0.10 (0.07-0.13)
Heterogeneity: I^2 = 75% (64%-83%); P < .01			
After 2007			
Ikeda et al,[55] 2015	1	81	0.01 (0.00-0.07)
Schreiner et al,[57] 2021	16	536	0.03 (0.02-0.05)
Katheria et al,[56] 2018	4	127	0.03 (0.01-0.08)
Galderisi et al,[63] 2019	2	50	0.04 (0.00-0.14)
Cimatti et al,[75] 2020	1	20	0.05 (0.00-0.25)
Alderliesten et al,[65] 2013	35	650	0.05 (0.04-0.07)
Martini et al,[61] 2022	5	77	0.06 (0.02-0.15)
Ishiguro et al,[59] 2014	7	92	0.08 (0.03-0.15)
Deshpande et al,[79] 2020	4	50	0.08 (0.02-0.19)
Vesoulis et al,[12] 2021	16	185	0.09 (0.05-0.14)
Jiang et al,[80] 2023	8	92	0.09 (0.04-0.16)
Duppré et al,[64] 2015	25	250	0.10 (0.07-0.14)
Katheria et al,[69] 2014	6	60	0.10 (0.04-0.21)
Hoffman et al,[85] 2019	7	61	0.11 (0.05-0.22)
Xing et al,[71] 2022	28	238	0.12 (0.08-0.17)
Juul et al,[73] 2020	107	906	0.12 (0.10-0.14)
Zanelli et al,[77] 2023	84	638	0.13 (0.11-0.16)
da Costa et al,[70] 2018	9	56	0.16 (0.08-0.28)
Vesoulis et al,[74] 2020	29	157	0.18 (0.13-0.25)
Bates et al,[76] 2016	22	108	0.20 (0.13-0.29)
June et al,[72] 2023	21	99	0.21 (0.14-0.31)
Noori et al,[68] 2014	5	23	0.22 (0.07-0.44)
Lampe et al,[81] 2020	56	254	0.22 (0.17-0.28)
El-Dib et al,[78] 2022	14	62	0.23 (0.13-0.35)
Naoshi et al,[86] 2021[a]	55	216	0.25 (0.20-0.32)
Farag et al,[82] 2022	34	132	0.26 (0.19-0.34)
Random-effects model		5220	0.11 (0.08-0.14)
Heterogeneity: I^2 = 87% (82%-90%); P < .01			
Random-effects model		8523	0.10 (0.08-0.13)
Prediction interval			(0.03-0.32)
Heterogeneity: I^2 = 83% (78%-87%); P < .01			
Test for subgroup differences: χ^2_1 = 0.18; P = .67			



Diamonds indicate overall proportions.

[a]Abstract presented at the 73rd Annual Congress of the Japan Society of Obstetrics and Gynecology.[86]

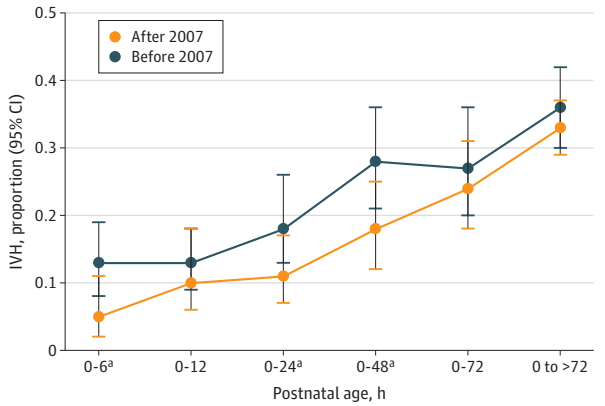
29%-48%) among the noncategorized studies (eFigure 1 in Supplement 1). There was no significant difference in the 3 subgroups.

In the studies after 2007, IVH occurrence was 41% (95% CI, 31%-52%) in infants with GA less than 28 weeks, 27% (95% CI, 20%-36%) in infants with GA less than 32 weeks, and 28% (95% CI, 20%-39%) in noncategorized studies. The difference between subgroups of GA less than 28 and less than 32 was significant. This finding is consistent with the expectations that IVH is inversely associated with the upper limit of GA as an inclusion criterion for studies (eFigure 2 in Supplement 1).

Occurrence of severe IVH in infants with GA less than 28 weeks, GA less than 32 weeks, and among the noncategorized studies in studies before 2007 was 18% (95% CI, 6%-43%), 7% (95% CI, 3%-15%), and 10% (95% CI, 7%-15%) (P = .04), respectively, whereas after 2007, it was 17% (95% CI, 11%-26%) (P < .001), 8% (95% CI, 5%-12%) (P < .001), and 12% (95% CI, 7%-19%) (P < .001), respectively (eFigure 3 and eFigure 4 in Supplement 1). This finding is consistent with the

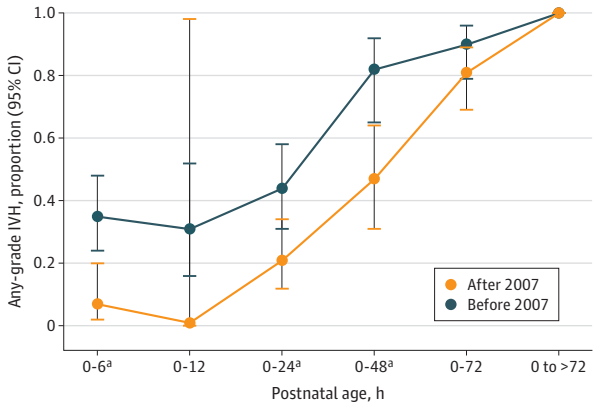
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Figure 4. Intraventricular Hemorrhage (IVH) Rate Among All Preterm Infants by Postnatal Age



[a]*P* < .05.

Figure 5. IVH Rate Among All Intraventricular Hemorrhage (IVH) Events by Postnatal Age



[a]*P* < .01.

expectations that the risk of severe IVH is inversely associated with GA.

Proportion of Any Grade IVH in All Preterm Neonates by Postnatal Age

The proportion of very early presenting IVH (up to 6 HOL) after 2007 was significantly lower than before 2007 (5% [95% CI, 2%-11%] vs 13% [95% CI, 8%-19%]). IVH up to 24 HOL before and after 2007 was 18% (95% CI, 13%-26%) and 22% (95% CI, 7%-17%) and up to 48 HOL, 28% (95% CI, 21%-36%) and 18% (95% CI, 12%-25%) among all preterm neonates, respectively. The proportions in the intervals 0 to 12 and 0 to 72, and beyond 72 HOL did not change significantly (**Figure 4**; eFigures 5-9 in Supplement 1). To highlight the accuracy of our results, 10[56,59,61-63,68,70,73,75,78] of 13 studies contained individual data in the subgroup after 2007.

Proportion of Any Grade IVH Among All IVH Events by Postnatal Age

The studies included reported IVH proportion in all IVH events before and after 2007 at different time intervals. The proportion of very early presenting IVH decreased significantly after 2007 (6 HOL: 35% [95% CI, 24%-48%] before 2007 vs 9% [95% CI, 3%-23%] after 2007; *P* = .002; 24 HOL: 44% [95% CI, 31%-58% before 2007 vs 25% [95% CI, 15%-39%] after 2007; *P* = .03; up to 48 HOL: 82% [95% CI, 65%-92%] before 2007 vs 50% [95% CI, 34%-66%] after 2007; *P* = .002). The remaining events occurred beyond 72 HOL (**Figure 5**; eFigures 10-14 in Supplement 1). To highlight the accuracy of our results, it should be emphasized that 6[59,61-63,68,75] of 9 studies contained individual data in the subgroup after 2007.

Differences in the Distribution Pattern of Onset of IVH of Any Grade by GA and Epochs

The distribution pattern showed no significant difference between neonates with GA less than 28 and GA less than 32 in studies after 2007 (eTable 3 and eFigures 15-19 in Supplement 1) nor in neonates with GA 32 weeks or less between the subgroups before and after 2007 (eFigures 20-24 in Supplement 1) nor in neonates with GA less than 28 weeks in the subgroups before and after 2007 (eFigures 25-29 in Supplement 1).

Risk of Bias Assessment

Twenty-eight studies[24,25,27,28,30,31,33-37,39,45,46,49-51,53,54,57,58,60,66,67,71,76,85,86] (44%) had an overall high risk of bias, whereas 17 studies[12,40,47,52,56,59,61,62,65,68,70,75,78,79,81,82,84] (27%) had a low risk of bias. The primary reasons for the significant risk of bias were the absence of information on participation and the lack of information on follow-up time (eTable 4 in Supplement 1).

Heterogeneity and Publication Bias

Variations in study methods, including differences in cranial ultrasonography timing and study populations, may explain the discrepancies in the exact timing of cranial ultrasonography. For this reason, we performed an additional subgroup analyses based on gestational age, early and total mortality, antenatal steroid use, outborn status, and exclusion criteria (eFigures 30-38 in Supplement 1). However, after all listed adjustments, heterogeneity remained unexplained.

Visualization and the corresponding Peter test *P* value suggest no publication bias in studies after 2007 (eFigure 40 and eFigure 42 in Supplement 1). However, for earlier studies, Peter test *P* value indicates potential publication bias (*P* = .04) (eFigure 39 and eFigure 41 in Supplement 1).

Discussion

Our systematic review and meta-analysis found that although the occurrence of IVH in preterm infants did not change over time, the time of onset of IVH shifted toward later in life. The very early presentation of IVH now accounts for less than 10% of all IVH events, decreasing 4-fold (35% vs 9%) in the years 2007 to 2023 compared with 1981 to 2006. However, the overall occurrence of any grade IVH and severe IVH has remained unchanged.

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Several factors play a role in the development of IVH, including antenatal, perinatal, and postnatal events. Although IVH is an acute event, the exact time of onset is unknown, as IVH is clinically silent[87] in most events, and in many places, the first cranial ultrasonography is performed beyond the third postnatal day. Some experts consider that IVH occurring before 12 hours of life may be associated with antepartum or intrapartum events, whereas those occurring after 12 hours of life are often associated with other postnatal factors.[28,29,34-36,53] Accordingly, the time of the onset of IVH is critical information that can help clinicians better understand the relationship between certain risk conditions and IVH and assess the value of preventive intervention.

Current recommendations on the timing and frequency of cranial ultrasonography do not support the diagnosis of the exact time of onset of IVH. The American Academy of Pediatrics recommends neurosonography in preterm infants within 7 days of birth.[88] Of the 64 articles studied, 56 studies[12,24,26-28,30-57,59-66,68,69,72-76,78-84,86] performed cranial ultrasonography within 24 HOL, and all 64 articles conducted cranial ultrasonography within 72 HOL. Some experts have emphasized the importance of detecting the onset of IVH by performing cranial ultrasonography several times during the first week rather than only once on days 7 to 10, arguing that this allows a better delineation of the timing of injury and identification of antecendence.[89]

In a comprehensive analysis by Lai et al[7] using data from 2010 to 2020, the incidence of IVH was 34.3%, and the incidence of severe IVH was 15.0% for infants with GA less than 28 weeks. The Vermont Oxford Network reported in 2023 that the rates of IVH and severe IVH remained stable since 2012.[90] Our study is not epidemiological, but our data are comparable to these epidemiological reports, indicating that we elaborate field data.

Al-Abdi et al[11] reported a higher proportion of IVH in preterm infants up to 6 HOL before 2007. This may be explained by differences in the study population, exclusion, and inclusion criteria. Our study was more stringent, excluding certain articles[31,36] and including others[26,30,40,50,52] compared with the study by Al-Abdi et al.[11] Due to relatively minor differences and the historical nature of the results before 2007, we do not consider this clinically relevant. In a 2019 study, Leiser et al[91] reported that the onset of IVH occurs at a mean of 24 to 48 hours after delivery, with approximately 10% developing within 12 hours after birth, which is consistent with our findings.

The unchanged overall prevalence of IVH may be surprising. There are several possible explanations for this result. One is that with advances in neonatology, although the incidence of IVH may have decreased in infants with GA 26 to 28 weeks, this may have been offset by an increase in more vulnerable infants with GA 22 to 25 weeks with a higher incidence of IVH. Thus, for the cohort as a whole, the rate of IVH did not change significantly. This explanation is partially supported by Horbar et al,[92] who reported that between 1997 and 2021, the mortality rate for extremely preterm infants decreased from 18.1% to 12.4% and distributions of infants by week of GA remained stable over the period. Similarly, our meta-analysis found that the pooled mean GA did not differ significantly between the 2 periods. However, we could not detect a similar reduction in mortality, as most of the articles included did not provide data on mortality and IVH by GA subgroups.

A further explanation may be that not all preventive measures to reduce IVH are currently well developed or consistently applied. However, the reduction in early IVH is an encouraging result. This may indicate a more consistent use of procedures with evidence of beneficial effects, eg, antenatal steroids, magnesium sulfate, delayed and physiological-based cord clamping, and thermal protection. Our meta-analysis is not well suited to prove this explanation in detail. However, it should be noted that all these measures may not be sufficient to completely eliminate and prevent IVH. Thus, the risk and susceptibility to IVH persist in the early days of life and may still occur due to respiratory and circulatory perturbation, pain, or other environmental stressors that are not yet sufficiently controlled.

Implications for Practice and Future Research

High heterogeneity was observed across studies, suggesting a need for standardized reporting of cranial ultrasonography and accurate documentation of risk factors for each patient. We hypothesize that, due to the multifactorial etiology of IVH, timely detection of IVH in preterm infants may help us to gain a deeper understanding of the specific roles of each contributing factor and pathomechanism. Accurate, timely diagnosis of IVH is possible with an increased frequency of cranial ultrasonography during the early days of life. However, this is contrary to the recommended minimal handling of the infants. Other neurointensive monitoring tools, such as electroencephalography,[49] near-infrared spectroscopy,[56,62,65,68,75,78,79] ongoing evolution of ultrasonographic technology,[93] or a combination of these, may promise more accurate, timely detection of IVH in the future. The translation of scientific research findings into clinical practice is crucial for the benefit of both clinicians and patients.[94,95]

Strengths and Limitations

In terms of strengths, our analysis followed a preregistered protocol, applying a rigorous method. The main strength of this study is the large amount of individual data used. It is essential to acknowledge that the time of detection is not equal to the real-time onset; however, on the basis of our results, it is reasonable to assert that before 6 HOL is a sufficiently narrow time window to support clinically relevant accuracy in detecting changes in the development of IVH.

This study also has some limitations. Several factors may influence the prevalence and the time of onset of IVH, such as GA, antenatal steroids, birth setting, and resuscitation protocol, along with different exclusion criteria and mortality reporting.[96-98] However, this study could not explore the specific role of these factors in the variation of IVH in different studies. Some experts point out that improved ultrasonography equipment with increased resolution allows the detection of more grade 1 IVH events.[91] If advanced cranial ultrasonography techniques have indeed allowed more accurate detection of IVH in recent years, this rather supports our observation that the proportion of very early IVH has declined robustly, while a small reduction in overall IVH may be missed.

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Conclusions

The findings of this systematic review and meta-analysis indicate that the overall prevalence of IVH did not change significantly over the past 20 to 40 years; however, the very early presenting form of IVH declined substantially. Less than 10% of all IVH in preterm infants occurred before 6 hours of life. These data suggest that recently implemented preventive measures have the potential to postpone rather than reduce IVH in very preterm infants.

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