Brain Tumor Pathology
https://doi.org/10.1007/s10014-026-00536-4

ORIGINAL ARTICLE

Prognostic significance of CDKN2A/B hemizygous deletion in *IDH*-mutant astrocytomas: a systematic review and meta-analysis

Satoshi Nakasu[1,6] · Shoichi Deguchi[2] · Mónica Mezmezian[3] · Koichi Mitsuya[4] · Akifumi Notsu[5] · Yoko Nakasu[4,6]

Received: 17 November 2025 / Accepted: 1 March 2026

Abstract

The prognostic significance of *CDKN2A/B* hemizygous deletion (HemD) in *IDH*-mutant astrocytomas (A-IDHm) remains unclear. We conducted a systematic review and WHO grade-specific meta-analysis of primary tumors following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Effect sizes included hazard ratios (HRs) and restricted mean survival time (RMST) for overall survival. The pooled frequency of HemD in grade 2 A-IDHm was 13.8% (95% confidence interval [CI]: 8.5–21.7%; 12 studies; I^2=23.6%), lower than that in grade 3 tumors (25.2% [CI: 20.5–30.5%; 12 studies; I^2=0%]) and grade 4 tumors with *CDKN2A/B* non-homozygous deletion (29.5% [CI: 23.3–36.6%]; 11 studies; I^2=0%). Stratification by WHO grade revealed a significant association in grade 2 tumors (pooled HR [pHR]: 1.98 [CI: 1.03–3.80]; four studies; 369 patients; P=0.04; I^2=0%), but no significant association in grade 3 (pHR: 1.78 [CI: 0.99–3.20]; five studies, 239 patients; P=0.054; I^2=0%) or grade 4 tumors (pHR: 1.39 [CI: 0.85–2.26]; five studies; 192 patients; P=0.18; I^2=0%). The RMST difference reached statistical significance only in WHO grade 2 tumors, suggesting a potential prognostic effect of HemD in low-grade A-IDHm.

Keywords *IDH*-mutant astrocytoma · CDKN2A/B · Hemizygous deletion · Meta-analysis

Introduction

The CDKN2A gene encodes a cyclin-dependent kinase inhibitor (p16) and a TP53 activator (p14). In many human cancers, *CDKN2A* is inactivated to varying degrees through promoter methylation, mutation, and homozygous deletion, depending on the tumor type [38]. Loss of function promotes malignant behavior through cell-cycle dysregulation, increased cell proliferation, and enhanced angiogenesis in vivo [8]. Tumors with loss of the 9p21 *(CDKN2A)* locus are characterized by a "cold" immune microenvironment with reduced expression of immunostimulatory genes [5, 29].

Homozygous deletion is the primary mechanism of *CDKN2A* silencing in gliomas [7, 13], and locus deletions commonly include the adjacent *CDKN2B* gene encoding p15 [38]. In *IDH*-mutant astrocytomas (A-IDHm), *CDKN2A/B* homozygous deletion (HoD) is rare in histologically grade (hG) II (WHO former grading) tumors but occurs in 11% and 39.5% of hGIII and hGIV tumors, respectively [24]. The presence of HoD is a criterion for classifying A-IDHm as WHO grade 4 [2] and is consistently associated with poor prognosis, except in hGII tumors, wherein evidence remains insufficient due to limited data [24].

The prognostic significance of *CDKN2A/B* hemizygous deletion (HemD) remains debated. Three studies published in 2023, primarily using data from the MSKCC, TCGA, and GLASS cohorts, demonstrated that HemD also carries prognostic significance (Supplementary Table 1) [13, 18, 35]. However, these studies assessed combined groups of

✉ Satoshi Nakasu
neuro-nakasu@kfx.biglobe.ne.jp

1 Division of Neurosurgery, Omi Medical Center, Yabase-cho 1660, Kusatsu, Shiga 525-8585, Japan

2 Department of Neurosurgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

3 Laboratory of Neuropathology and Molecular Biology, Fleni, Buenos Aires, Argentina

4 Division of Neurosurgery, Shizuoka Cancer Center, Nagaizumi, Japan

5 Clinical Research Center, Shizuoka Cancer Center, Nagaizumi, Japan

6 Department of Neurosurgery, Shiga University of Medical Science, Ohtsu, Japan

Published online: 17 March 2026

A-IDHm regardless of histological grade. If the frequency of HemD increases with histological grade, as is the case with HoD, its true prognostic value can be accurately determined only through grade-specific analysis. Additionally, two of these studies included specimens obtained at the time of tumor recurrence, which might further complicate the evaluation of the prognostic significance of HemD. In 2024, Ghisai et al. [9] reported no significant difference in the survival outcomes of patients with mostly hGIII tumors in the CATNON cohort. In contrast, Ghosh et al. [10] reported that, compared with patients with nondeleted (nonD) tumors, patients with WHO grades 2–3 A-IDHm and HemD, including those with recurrent disease, experienced worse survival (see summary in Supplementary Table 1).

A WHO grade-specific analysis of primary tumors conducted by Ippen et al. [16] demonstrated no significant prognostic effect of HemD in WHO grade 2 ($P = 0.496$) and grade 3 ($P = 0.23$) A-IDHm. This observation is consistent with the negative results reported by subsequent studies, including Mezmezian et al. [22] in WHO grade 2 ($P = 0.08$) and Lasica et al. [19] in grade 4 astrocytomas ($P = 0.175$).

The present review aimed to determine the prognostic significance of HemD in primary A-IDHm. Following a systematic review, eligible studies were subjected to meta-analysis. First, we examined the frequency of HemD across WHO grades to assess whether its prevalence increases with grade. Next, we evaluated the prognostic implications of HemD stratified by WHO grade.

Materials and methods

The present study, which is part of a previously registered protocol (CRD42024570409) designed to investigate the prognostic role of CDKN2A/B alterations—including HoD and HemD—in A-IDHm, was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Literature search and data extraction

The initial search was conducted on August 1, 2024, as described by Nakasu et al. [24]. Articles published in English since 2009 were identified using the keywords "glioma," "astrocytoma," or "glioblastoma" combined with "IDH*," "CDKN2*," "p16," "INK4*," or "p15" across PubMed, Ovid MEDLINE, and Scopus. As approximately 12 months had elapsed since the initial search, an updated search was conducted on July 10, 2025 (Fig. 1; Supplementary Table 2). Searches were conducted independently by two authors. Eligible studies reported data on HemD and either patient numbers or survival outcomes stratified by WHO grade. Studies including ≥ 20 adult patients (age ≥ 18 years) with A-IDHm without 1p/19q codeletion were included. Studies enrolling a small number of adolescent patients were also accepted. EndNote (version 20; Clarivate, Philadelphia, PA, USA) was used for reference management. Exclusion criteria were as follows: (1) failure to distinguish data from recurrent tumors, (2) analyses based solely on public databases (to avoid overlap with institutional datasets) (3) absence of required molecular data, or (4) focus on familial or pediatric cancers. When multiple studies originated from the same institution, the most recent or most relevant study was selected. Final study selection was determined through discussion and consensus among the authors.

Data on patient age and sex, WHO grade, year of publication, molecular characteristics, and survival outcomes were collected and independently verified multiple times by the authors. When the mean age was unavailable, it was estimated using the median using the method described by Hozo et al. [14]. WHO grades were reclassified based on histological grading together with *CDKfN2A/B* status. Individual patient data (IPD) were extracted when available, and relevant statistical data were recalculated from the IPD. WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/) was used as described previously [23] to extract individual survival data from Kaplan–Meier curves. Data extraction was repeated until reconstructed curves closely overlapped with the original curves. Differences in P-values from the log-rank test were within 5% of the reported values. The corresponding author of one study provided additional required data [22]. Hazard ratios (HRs) and restricted mean survival time (RMST) for overall survival (OS) were used as effect measures in two- and one-stage meta-analyses, respectively.

Statistical analysis

Statistical analyses were performed using R (version 4.4.2 (https://www.r-project.org/). The frequency of HemD in each WHO grade subgroup was assessed using the *metaprop* function within a generalized linear mixed-effects model. Between-study heterogeneity was assessed using I^2 statistics, τ^2, and prediction intervals.

Based on Kaplan–Meier curves reconstructed from IPD, survival analyses were performed using log-rank tests and Cox proportional hazards models in the EZR graphical interface. Meta-analyses of HRs were conducted using an inverse-variance approach with a random-effects model (two-stage meta-analysis). RMST was calculated from synthesized Kaplan–Meier curves derived from IPD (one-stage meta-analysis). Time–RMST difference curves were constructed to interpret the summary differences, considering the difficulty of defining an appropriate truncation time in

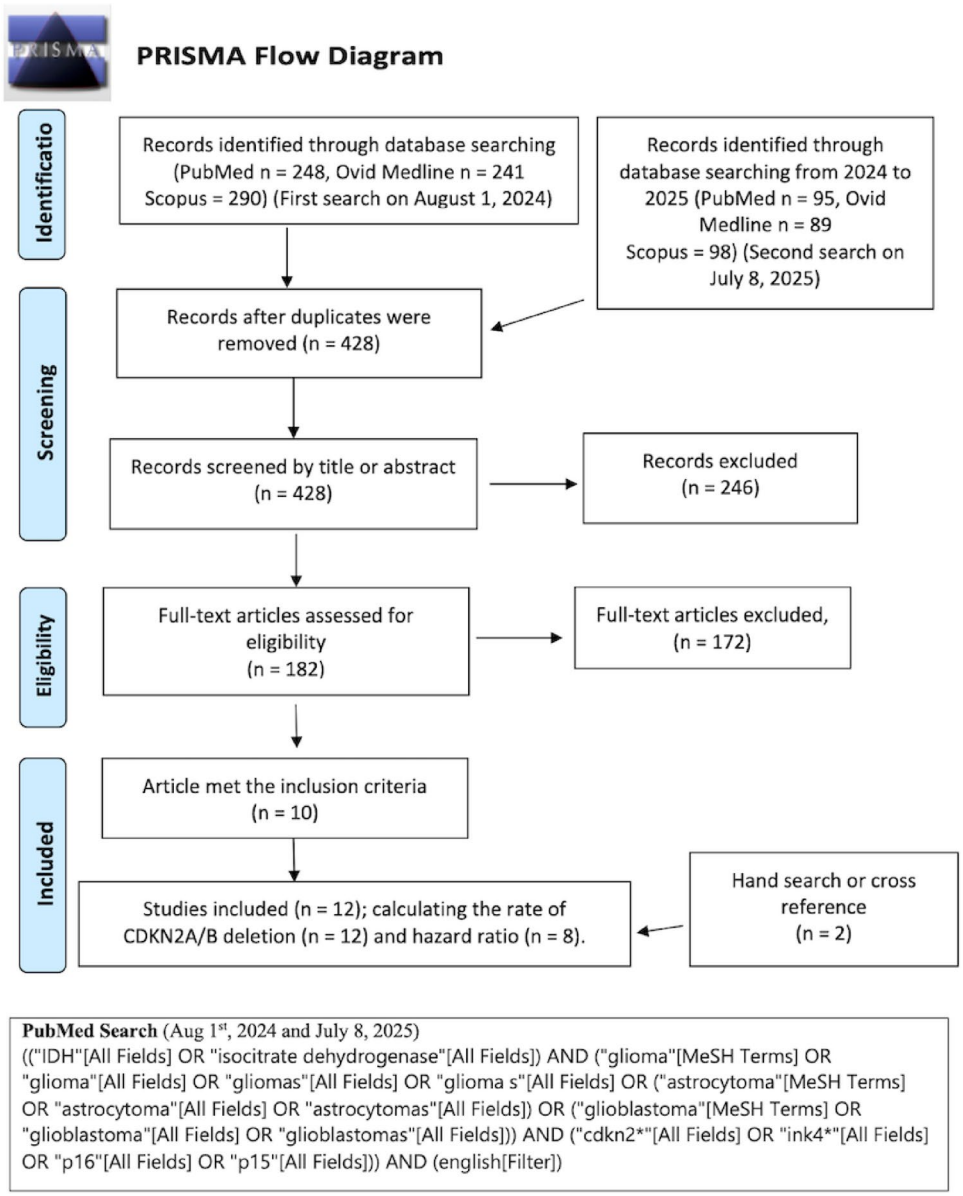

Fig. 1 PRISMA flow diagram and search strategy used in PubMed

glioma studies. RMST was calculated using the survRM2 package in R.

All HRs were derived from univariate analyses. After pooling survival data across all grade groups for patients with HemD and nonD, survival outcomes were compared within each WHO grade. A P value of <0.05 was considered statistically significant.

Risk of bias

Risk of bias was assessed using the Joanna Briggs Institute critical appraisal checklist for case series (https://jbi.global/critical-appraisal-tools) (Supplementary Table 3). P ublication bias in frequency studies was evaluated using a Doi plot and the Luis Furuya-Kanamori (LFK) index, as conventional funnel plots may be inadequate for proportional data [15]. For HR analyses, linear regression–based assessments of publication bias were not performed because of the limited number of included studies.

Ethical approval and informed consent

This review did not involve direct research involving human participants.

Results

Literature search and data extraction

After removal of duplicates, 428 records were identified from PubMed, Ovid MEDLINE, and Scopus. Following title and abstract screening, 246 records were excluded (Fig. 1). Full-text review of the remaining 182 studies identified 10 that met the inclusion criteria. Excluded articles comprised review or editorial papers (n = 19), public database studies (n = 11), studies including fewer than 20 patients (n = 27), studies including recurrent tumors (n = 10), studies lacking extractable data (n = 73), studies with overlapping datasets (n = 5), and studies excluded for other reasons (n = 36). Two additional studies were identified through manual reference screening. Data from the final 12 studies are summarized in Table 1 and Supplementary Table 4 [1, 6, 12, 16, 19, 21, 22, 25, 28, 33, 36, 39]. All 12 studies were included in the frequency analyses, and 8 were included in the survival analyses. Seven studies evaluated both *CDKN2A* and *CDKN2B*, four focused exclusively on *CDKN2A*, and one evaluated either both *CDKN2A* and *CDKN2B* or *CDKN2A* alone (Supplementary Table 4). Major excluded large studies based primarily on public databases are summarized in Supplementary Table 1.

Survival data stratified by WHO grade were available from six studies through Kaplan–Meier curves or IPD.

Risk of bias assessment

Most included studies were retrospective case series with low levels of evidence (Supplementary Table 3). Although consecutive participant inclusion was often not explicitly stated in multicenter studies, the overall risk of bias was considered to be acceptable.

Frequency of HemD

The pooled frequency of HemD in WHO grade 2 A-IDHm was 13.8% (95% confidence interval [CI]: 8.5–21.7%; 12 studies; Table 2; Fig. 2a), with mild heterogeneity (I^2 = 23.6%; τ^2 = 0.47). Minor publication bias was suggested by the Doi plot (LFK index = − 1.78; Supplementary Fig. 1A).

The pooled frequency of HemD in WHO grade 3 tumors was 25.2% (CI: 20.5–30.5%; 12 studies), with no observed

Table 1 Summary data for selected studies

Author, year	*N*	Age (range)	sex (M/F)	WHO grade 2/3/4	G4nonHoD	method	threshold for HoD	threshold for HemD	Survival data
Eckel-Passow (2015)	45	m37	NA	30/9/6	NA	FISH	NA	NA	NA
	111	m38	NA	43/42/26	15	CGH	NA	NA	NA
Arita (2016)	94	m41.6 (21–78)	51/43	42/38/14	7	MLPA	NA	NA	IPD
Shirahata (2018)	211	m37.6 (15–70)	130/81	54/75/82	44	Meth	log2 ≤ −0.415	NA	K–M, IPD
Zschernack (2023)	21	m39.2 (20–56)	NA	2/15/4	1	MLPA, MIP	NA	NA	NA
Maragkou (2023)	25	m40.0 (22–60)	14/11	10/7/8	4	Meth	log2≤ −0.4	NA	NA
Hayashi (2024)	21	NA (17–90)	NA	7/6/8	5	MLPA	x < 0.4	0.4 < x < 0.7	NA
Xi (2024)	114	m38	NA	42/33/39	14	FISH	15%	NA	K–M
Otsuji (2024)	52	M34.5 (19–71)	34/18	28/21/3	NA	MLPA	1 − Tumor cell rate × 0.75	1 – Tumor cell rate × 0.25	HR, K–M
Ippen (2025)	215	*m38.1 (14–70)	*95/78	98/75/42	23	Meth	By visual inspection**	By visual inspection **	K–M (sFig.1B)
Lasica (2025)	128	M37.1 (19–78)	79/49	0/0/107	86	CMA, NGS, FISH	10% for FISH	15% for FISH	K–M
Mezmezian (2025)	189	M35 (17–71)	101/88	133/18/38	21	Multiplex PCR	CDKN/GAPDH ratio < 0.4	0.4 < CDKN/GAPDH ratio < 0.7	IPD
Yuile (2025)	66	m38.6 (20–74)	36/30	14/31/21	9	NGS, FISH Meth, SNP	NA	NA	K–M

M median, *m* mean, *M/F* male and female, *NA* not available, *G* WHO grade, *G4nonHoD* grade 4 tumors without CDKN2A/B homozygous deletion, *HemD* hemizygous deletion, *FISH* fluorescence in situ hybridization, *NGS* next generation sequencing, *Meth* DNA methylation analysis, *MLPA* multiplex ligation dependent probe amplification, *MIP* molecular inversion probe assay, *SNP* single nucleotide polymorphism array, *CGH* comparative genomic hybridization, *CMA* chromosome microarray analysis, *IPD* individual patient data, *K–M* Kaplan–Meier curve

*Data for grade 2 and 3 tumors

**The *CDKN2A*/B locus was assessed by visually inspecting copy-number plots from methylation-array data for each case. A hemizygous loss was identified if the locus showed a signal equivalent to single-copy chromosomal losses; a homozygous loss was defined if the signal was twice as deep as that of single-copy changes

Table 2 Pooled frequency and hazard ratio of *CDKN2A/B* hemizygous deletion in IDH mutant astrocytomas

WHO grade	Frequency [95%CI], (PI)	Difference of frequency	Pooled hazard ratio for OS
Grade 2	13.8% [8.5–21.7], (3.0–45.0), I^2 = 23.6% 12 studies, *N* = 503	Grade 2 vs. Grade 3 ***P*** **= 0.017**	1.98 [1.03–3.80], *P* = **0.04**, I^2 = 20.4%, 4 studies, *N* = 369
Grade 3	25.2% [20.5–30.5], (17.9–34.1), I^2 = 0% 12 studies, *N* = 370	Grade 3 vs. Grade 4 *P* = 0.30	1.78 [0.99–3.20], *P* = 0.054, I^2 = 0%, 5 studies, *N* = 239
Grade 4 without HoD	29.5% [23.3–36.6], (21.3–39.4), I^2 = 0%, 11 studies, *N* = 229		1.39 [0.85–2.26], *P* = 0.18, I^2 = 8.4%, 5 studies, *N* = 192

N patient number, *CI* confidence interval, *PI* prediction interval, *OS* overall survival, *HoD* CDKN2A/B homozygous deletion, Bold, statistically significant

heterogeneity (I^2 = 0%; Table 1; Fig. 2a). Doi plots indicated publication bias (LFK index = −2.01; major asymmetry; Supplementary Fig. 1B).

For WHO grade 4 tumors, the frequency after excluding HoD tumors (163 HoD among 392 grade 4 tumors) was calculated. The pooled frequency was 29.5% (CI: 23.3–36.6%; 11 studies), with low heterogeneity (I^2 = 0%, Fig. 2a) and minimal publication bias (LFK index = 1.08; Supplementary Fig. 1 C). When HoD tumors were included, the pooled frequency was 17.2% (CI: 13.8–21.3%; 11 studies).

Subgroup analyses revealed a significantly lower HemD frequency in grade 2 tumors than in grade 3 tumors (*P* = 0.017), but no significant difference between grade 3 tumors and grade 4 tumors without HoD (*P* = 0.30). No significant subgroup differences were observed based on detection method (fluorescence in situ hybridization [FISH] vs. non-FISH vs. mixed), geographic region (Asia vs. non-Asia), or whether *CDKN2A* alone versus *CDKN2A/B* was assessed (Supplementary Table 5).

Sensitivity analyses using a leave-one-out approach indicated minimal variation in pooled estimates: 13.3–16.9% for WHO grade 2, and 23.4–26.9% for WHO grade 3, and 28.5–33.6% for grade 4 tumors (Supplementary Fig. 2). When studies reporting WHO grade-specific data that included fewer than 20 cases of A-IDHm were included, the pooled frequency of HemD in grades 2, 3, and 4 without HoD changed only marginally—from 13.8% to 14.1%, from 25.2% to 25.1%, and from 29.5% to 29.8%, respectively (Supplementary Fig. 4).

Differences in clinical characteristics of nonD and HemD tumors

No significant differences were observed between patients with nonD and HemD tumors with respect to age (standardized mean difference: 0.15; CI: −0.034 to 0.34; seven studies; *P* = 0.11), sex (pooled odds ratio: 1.30; CI: 0.80–2.10; seven studies; *P* = 0.29), or MGMT promoter methylation status (pooled odds ratio: 0.62; CI: 0.29–1.34; three studies; *P* = 0.23). Treatment-related factors were not analyzed because of the lack of data.

OS

Among the eight studies included in the survival analyses, three were multi-institutional and did not clearly specify whether patient enrollment was consecutive or comprehensive (Supplementary Table 3).

Across all WHO grades combined, survival outcomes in A-IDHm were significantly worse in patients with HemD tumors than in those with nonD tumors (pooled HR: 1.73; CI: 1.28–2.32; prediction interval: 1.21–2.7; eight studies; *P* = 0.0003; I^2 = 0%; Fig. 2b). Publication bias was minimal (LFK index = 1.08; Supplementary Fig. 1D). As HemD was less frequent in WHO grade 2 tumors than in higher-grade tumors, tumor grade could confound the survival analyses. To address this potential confounding, subsequent analyses were performed separately for each WHO grade to assess the prognostic effect of HemD within grades. In WHO grade 4 tumors, survival comparisons between patients with nonD and HemD tumors were conducted in the same approach as that for grades 2 and 3.

In WHO grade 2 tumors, HemD was associated with a poorer OS (pooled HR: 1.98; CI: 1.03–3.80; four studies; *P* = 0.04; I^2 = 20.4%; Table 2, Supplementary Fig. 3A). No significant associations were observed for grade 3 (pooled HR: 1.78; CI: 0.99–3.20; five studies; *P* = 0.054; I^2 = 0%; Supplementary Fig. 3B) or grade 4 tumors without HoD (pooled HR: 1.39; CI: 0.85–2.26; five studies; *P* = 0.18; I^2 = 8.4%; Supplementary Fig. 3 C; Table 2).

Kaplan–Meier analyses based on IPD showed median OS of 234 versus 143 months for patients with grade 2 nonD and HemD tumors (log-rank test *P* = 0.019; Fig. 3a), 140 versus 108 months for patients with grade 3 nonD and HemD tumors (*P* = 0.19; Fig. 3c), and 85 versus 71.4 months for patients with grade 4 nonD and HemD tumors, respectively (*P* = 0.22; Fig. 3e). In WHO grade 2 tumors, RMST differences between nonD and HemD groups emerged after 210 months, reaching a 28-month difference at 216 months (approximately 18 years; HemD: 140 months; CI: 114.4–165.6; nonD: 168.1 months; CI: 156.6–179.6; *P* < 0.05; Fig. 3b; Table 3). In grade 3 tumors, RMST difference decreased to −14 months from −0.05 months during the first 10 years; however, the CI did not cross zero (*P* = 0.06–0.09; Fig. 3d). No significant RMST difference was observed in grade 4 tumors (Fig. 3f). Notably, patients with grade 4 HoD tumors had a significantly shorter median OS (36 months; CI: 29.3–56.0) than those with HemD (71.4

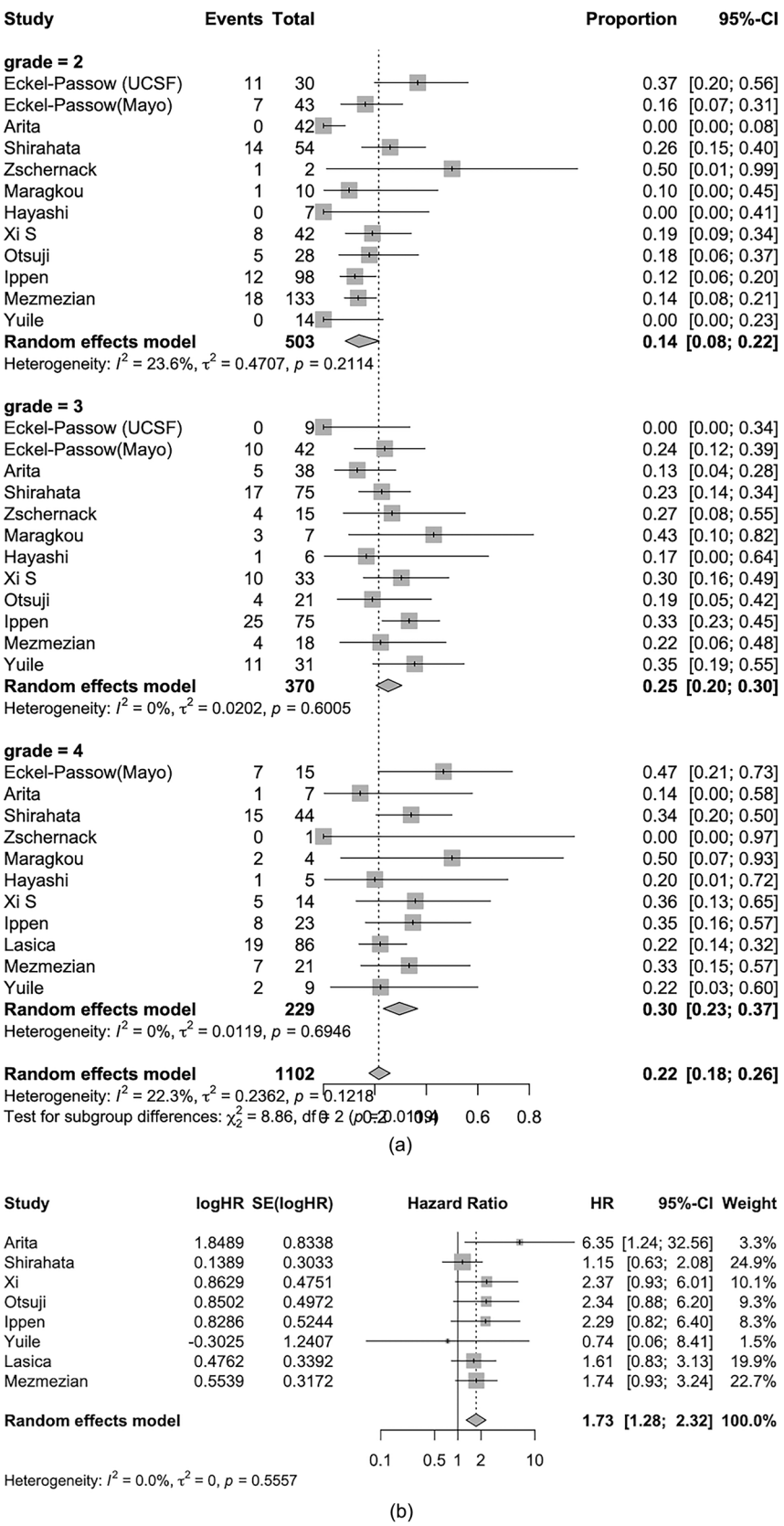

Fig. 2 Pooled frequency of *CDKN2A/B* hemizygous deletion (HemD) in *IDH*-mutant astrocytomas (A-IDHm) (**a**). Pooled hazard ratio for HemD in A-IDHm across all WHO grades (**b**). *HR* hazard ratio, *SE* standard error

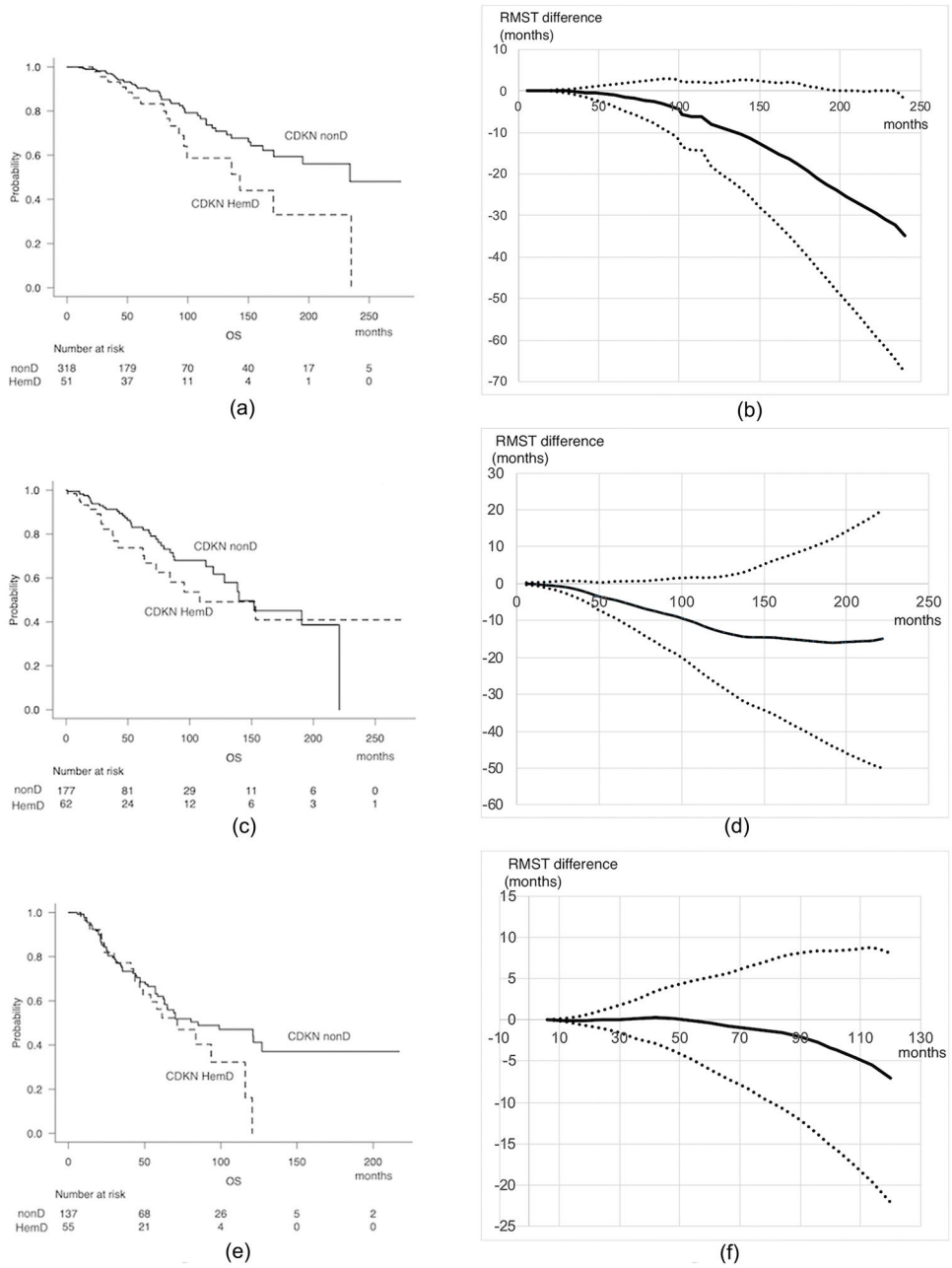

Fig. 3 Kapan–Meier curves for WHO grade 2 (**a**), grade 3 (**c**), and grade 4 tumors (**e**). Time-restricted mean survival time (RMST) difference curves for WHO grade 2 (**b**), grade 3 (**d**), and grade 4 tumors (**f**). Dotted lines indicate 95% confidence intervals. *nonD* no deletion, *HemD* hemizygous deletion, *OS* overall survival

months; CI: 46.7–116; $P=0.026$, post-hoc Bonferroni test) or nonD tumors (85.1 months; CI: 63.0–127.0; $P<0.0001$).

Discussion

This systematic review and meta-analysis is the first to evaluate the prognostic significance of HemD in A-IDHm. Although several large public datasets have examined the prognostic role of HemD [10, 13, 18, 35], many overlap with institutional data included in our analyses and either lack WHO grade-specific information or include recurrent tumors (Supplementary Table 1). Our findings indicate that HemD is an important negative prognostic marker for survival in A-IDHm across all tumor grades, a pattern that is partly attributable to the lower frequency of HemD observed in WHO grade 2 tumors than in higher-grade tumors. NonD tumors were more common in grade 2 cases and were associated with a more favorable prognosis. Grade-specific assessments revealed a negative prognostic effect of HemD in grade 2 tumors, whereas no substantial prognostic influence was observed in higher-grade tumors.

Table 3 Restricted mean survival time in the synthesized Kaplan–Meier curves

	RMST 60 months	RMST 120 months	RMST 18 years
G2 nonD	58.1 [57.2–59.0]	107.9 [104.3–111.5]	168.1 [156.6–179.6]
G2 HemD	57.0 [54.5–59.5]	99.8 [90.5–109.2]	140.0 [114.4–165.6]
Difference (months)	−1.1 [−3.8–1.6], $P=0.44$	−8.1 [−18.1 − 1.9], $P=0.11$	−28.1 [−56.2–−0.04], $P<0.05$
G3 nonD	51 [46.5–55.5]	98.6 [92.1–105.1]	143.6 [125.7–161.5]
G3 HemD	55.5 [53.5–57.5]	86.0 [73.5–98.6]	128.1 [99.5–156.6]
Difference (months)	−4.5 [−9.5–−9.5] $P=0.075$	−12.6 [−26.7–1.6] $P=0.08$	−15.5 [−49.2–18.2] $P=0.37$
G4 nonD	48.9 [46.0–51.9]	79.2 [71.2–87.1]	
G4 HemD	48.5 [43.8–53.3]	72.2 [59.3–85.0]	
Difference (months)	−0.4 [−6.0–5.2] $P=0.89$	−7.0 [−22.1–8.1] $P=0.36$	

RMST restricted mean survival time, *G2* WHO grade 2, *G3* WHO grade 3, *G4* WHO grade 4, *nonD* non *CDKN2A/B* deletion, *HemD CDKN2A/B* hemizygous deletion, [] 95% confidence interval

Frequency of HemD in A-IDHm

An increased frequency of HoD has been associated with higher histological grade [24]; however, potential relationships with HemD have been less well studied. In our analysis, HemD was less frequent in WHO grade 2 A-IDHm (13.8%) than in higher-grade tumors. Although HemD frequency appeared lower in WHO grade 4 tumors (17.2%) than in grade 3 tumors (25.2%) when all cases were considered, this finding was attributable to the high prevalence of HoD (approximately 40%) in grade 4 tumors. However, when HoD cases were excluded, HemD remained relatively frequent (29.5%) in grade 4 tumors. This subset represents histologically grade IV tumors without HoD, forming a distinct subgroup within the broader WHO 2021 grade 4 classification.

Diagnostic methods for CDKN2A/B HemD

A limitation of this analysis is the variation in diagnostic methods used to detect HemD across included studies (Table 1). Nevertheless, the heterogeneity (I^2) in pooled HemD frequency was low, indicating that most interstudy differences fell within the expected statistical variability. FISH may underestimate HoD because of the relatively large probe sizes, which can generate false negatives from probe redundancy or failure to detect microdeletions [3, 30].

Recent studies comparing methods for detecting HoD have reported high overall concordance in most cases [20, 30, 31]. Li et al. [20] reported strong agreement between FISH and next-generation sequencing (NGS) for assessing CDKN2A deletion status, with an area under the curve of 0.937 using a 23% FISH cutoff. Wang et al. [31] reported overall agreement rates of 85.7% between FISH (30% threshold) and NGS and 86.9% between FISH and DNA methylation microarray (DMM). Notably, among eight discordant cases, FISH detected HoD of CDKN2A/B, whereas six cases were classified as HemD when assessed using NGS or DMM. Therefore, threshold selection for defining deletion remains a challenge. As the tumor cell content influences optimal cutoff values, some authors adjusted thresholds according to tumor cell proportion [25]. However, most studies applied a fixed threshold after selecting areas with sufficient tumor cell content. Misclassification between HoD and HemD or between HemD and nonD may artificially exaggerate the apparent prognostic differences between hemizygous-deleted and nondeleted tumors.

Survival analysis

For survival analysis, we used pooled HRs and RMST. Although HR has traditionally been used as the effect measure in time-to-event meta-analyses, the assumption of proportional hazards may not hold across studies because of differences in follow-up duration and censoring patterns [11, 32, 37]. Therefore, IPD were combined to generate synthesized Kaplan–Meier curves for RMST calculation. Although pooling data from multiple studies may be influenced by outliers, pooled HRs from the two-stage meta-analysis demonstrated low heterogeneity across WHO grades.

Considering the lack of consensus regarding an appropriate truncation time in glioma studies, the truncation period can be set sufficiently long to allow RMST to approximate mean survival time. However, survival estimates near the final time points, when few patients remain at risk, exhibited considerable variability. Accordingly, time–RMST difference curves were constructed to facilitate interpretation [24, 37].

In patients with WHO grade 2 tumors, the RMST difference between HemD and nonD tumors increased with longer follow-up and reached statistical significance after 210 months, which is consistent with the observed results of pooled HR. Xi et al. proposed reclassification of grade 2 IDH-mutant astrocytomas with HemD as grade 3 [33]. However, in our study, survival differences between nonD and HemD grade 2 tumors were not statistically significant at 10–15 years, and the 15–18-year RMST results should be considered exploratory because of limited data and potential informative censoring. Additional evidence is required before definitive conclusions can be drawn.

In grade 3 tumors, the RMST difference remained just below statistical significance until 120 months and became increasingly uncertain thereafter because of the small number of patients at risk. Considering the pooled HR result for grade 3 ($P=0.054$), additional data are necessary to draw firm conclusions. In grade 4 tumors, no prognostic differences were observed between pooled HR and RMST, suggesting that the prognostic effect of HemD may vary by WHO grade.

The mechanisms by which HemD affects tumor behavior remain under investigation in gliomas and other cancer subtypes. In non–central nervous system cancers [4, 17], *CDKN2A/B* has been proposed to exhibit haploinsufficiency, whereby hemizygous loss reduces functional protein expression. Promotor methylation may further suppress gene function in HemD tumors [25, 27], and some A-IDHm tumors with HemD lack p16 expression [25, 26]. Alternatively, HemD tumors may have an increased likelihood of progression to HoD.

Limitations

One limitation of this meta-analysis is that all included studies were retrospective and therefore provided relatively low levels of evidence. Mild heterogeneity and publication bias were observed, likely reflecting the absence of standardized diagnostic methods and threshold definitions for HemD detection.

Another limitation is that HRs and RMST were partly calculated from data extracted from Kaplan–Meier curves. Although reconstructed curves closely overlapped with the originals, log-rank testing revealed small differences in P-values (within 5% of reported values).

Our survival analysis did not fully account for potential confounding factors associated with HemD. Age, sex, and MGMT promoter methylation status did not differ significantly between HemD and nonD groups. Among molecular alterations relevant to glioma grading, only HemD was evaluated in this study. Other prognostic molecular factors associated with HemD remained to be clarified. Amplifications of PDGFRA and CDK4/6 are potential risk factors in A-IDHm [16, 28, 34]. Although these alterations are generally mutually exclusive with HoD [34], their association with HemD remains unclear. High copy number variation load, MYCN amplification [28], and chromosome 7 trisomy [22] have also been associated with poor prognosis. Thus, comprehensive multivariable analyses are required before HemD can be reliably applied in clinical practice.

Although we excluded treatment-related variables from the analysis, therapeutic strategies are typically standardized within each WHO grade category. WHO grade-specific analyses may partially address this limitation; however, some patients were treated based on earlier WHO classifications, which may have introduced variability across cohorts.

Conclusion

This systematic review and meta-analysis indicates that HemD has a prognostic utility in A-IDHm, partly attributable to its lower frequency in WHO grade 2 tumors. WHO grade–stratified analyses revealed distinct patterns: a probable prognostic effect was observed in WHO grade 2 tumors, a less consistent association in grade 3 tumors, and no significant differences between patients with HemD and nonD tumors in WHO grade 4 tumors.

These findings are based on studies with limited levels of evidence. The independence of HemD from other adverse genomic alterations remains uncertain because most analyses did not adjust for these factors. Therefore, HemD should currently be considered a potential risk modifier, particularly in WHO grade 2 tumors, rather than a definitive prognostic marker. Prospective, multivariable studies incorporating comprehensive molecular profiling and standardized methods and thresholds are required before HemD can be incorporated into routine clinical decision-making or grading frameworks.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10014-026-00536-4.

Acknowledgements The authors would like to thank Enago (www.enago.jp) for the English language review.

Funding No specific grant was received for this study.

Data availability The data used in this study will be made available upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Arita H, Yamasaki K, Matsushita Y et al (2016) A combination of TERT promoter mutation and MGMT methylation status predicts clinically relevant subgroups of newly diagnosed glioblastomas. Acta Neuropathol Commun 4:79. https://doi.org/10.1186/s40478-016-0351-2
2. Brat DJ, Cahill DP, Cimino PJ et al (2021) Astrocytoma, IDH-mutant. In: board tWcote (ed) WHO classification of tumours: central nervous system tumours 5th edition International Agency for Research on Cancer, Lyon, pp 19–27

3. Broggi G, Barresi V (2023) Assessment of CDKN2A/B homozygous deletion in gliomas: to FISH or not to FISH? J Neuropathol Exp Neurol 82:742–744. https://doi.org/10.1093/jnen/nlad045
4. Chapman EJ, Harnden P, Chambers P et al (2005) Comprehensive analysis of CDKN2A status in microdissected urothelial cell carcinoma reveals potential haploinsufficiency, a high frequency of homozygous co-deletion and associations with clinical phenotype. Clin Cancer Res 11:5740–5747. https://doi.org/10.1158/1078-0432.Ccr-05-0411
5. Deng C, Li ZX, Xie CJ et al (2024) Pan-cancer analysis of CDKN2A alterations identifies a subset of gastric cancer with a cold tumor immune microenvironment. Hum Genomics 18:55. https://doi.org/10.1186/s40246-024-00615-7
6. Eckel-Passow JE, Lachance DH, Molinaro AM et al (2015) Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med 372:2499–2508. https://doi.org/10.1056/NEJMoa1407279
7. Ferreira WA, Araujo MD, Anselmo NP et al (2015) Expression analysis of genes involved in the RB/E2F pathway in astrocytic tumors. PLoS One 10:e0137259. https://doi.org/10.1371/journal.pone.0137259
8. Fortin Ensign SP, Jenkins RB, Giannini C et al (2023) Translational significance of CDKN2A/B homozygous deletion in isocitrate dehydrogenase-mutant astrocytoma. Neuro Oncol 25:28–36. https://doi.org/10.1093/neuonc/noac205
9. Ghisai SA, van Hijfte L, Vallentgoed WR et al (2024) Epigenetic landscape reorganisation and reactivation of embryonic development genes are associated with malignancy in IDH-mutant astrocytoma. Acta Neuropathol 148:50. https://doi.org/10.1007/s00401-024-02811-0
10. Ghosh HS, Patel RV, Claus EB et al (2024) Canonical amplifications and *CDKN2A/B* loss refine IDH1/2-mutant astrocytoma prognosis. Neuro Oncol 25:993–1003. https://doi.org/10.1093/neuonc/noae258
11. Hasegawa T, Misawa S, Nakagawa S et al (2020) Restricted mean survival time as a summary measure of time-to-event outcome. Pharm Stat 19:436–453. https://doi.org/10.1002/pst.2004
12. Hayashi T, Tateishi K, Matsuyama S et al (2024) Intraoperative integrated diagnostic system for malignant central nervous system tumors. Clin Cancer Res 30:116–126. https://doi.org/10.1158/1078-0432.CCR-23-1660
13. Hickman RA, Gedvilaite E, Ptashkin R et al (2023) *CDKN2A/B* mutations and allele-specific alterations stratify survival outcomes in IDH-mutant astrocytomas. Acta Neuropathol 146:845–847. https://doi.org/10.1007/s00401-023-02639-0
14. Hozo SP, Djulbegovic B, Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5:13. https://doi.org/10.1186/1471-2288-5-13
15. Hunter JP, Saratzis A, Sutton AJ et al (2014) In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. J Clin Epidemiol 67:897–903. https://doi.org/10.1016/j.jclinepi.2014.03.003
16. Ippen FM, Hielscher T, Friedel D et al (2024) The prognostic impact of *CDKN2A/B* hemizygous deletions in IDH-mutant glioma. Neuro Oncol 27:743–754. https://doi.org/10.1093/neuonc/noae238
17. Irving JA, Bloodworth L, Bown NP et al (2005) Loss of heterozygosity in childhood acute lymphoblastic leukemia detected by genome-wide microarray single nucleotide polymorphism analysis. Cancer Res 65:3053–3058. https://doi.org/10.1158/0008-5472.Can-04-2604
18. Kocakavuk E, Johnson KC, Sabedot TS et al (2023) Hemizygous CDKN2A deletion confers worse survival outcomes in IDHmut-noncodel gliomas. Neurooncol 25:1721–1723. https://doi.org/10.1093/neuonc/noad095
19. Lasica AB, Lan Z, Miller JJ et al (2025) Clinical, molecular and radiological predictors of prognosis in newly diagnosed astrocytoma, IDH-mutant, WHO grade 4. Neurooncol 27:2382–2398. https://doi.org/10.1093/neuonc/noaf133
20. Li H, Luo N, Fan C et al (2025) Assessment of CDKN2A homozygous and heterozygous deletions in gliomas across multiple detection platforms. BMC Cancer 25:1007. https://doi.org/10.1186/s12885-025-14266-x
21. Maragkou T, Reinhard S, Jungo P et al (2023) Evaluation of MTAP and p16 immunohistochemical deficiency as surrogate marker for CDKN2A/B homozygous deletion in gliomas. Pathology 55:466–477. https://doi.org/10.1016/j.pathol.2023.01.005
22. Mezmezian MB, Arakaki N, Diez B et al (2025) Impact of 10q loss, CDKN2A deletions, EGFR amplification, and trisomy of chromosome 7 in the overall survival of IDH-mutant astrocytoma. Clin Neuropathol 44:136–142. https://doi.org/10.5414/np301667
23. Nakasu S, Deguchi S, Nakasu Y (2024) Frequency and prognostic impact of CDKN2A/B alteration in oligodendrogliomas: systematic review and meta-analysis. Neurol Med Chir (Tokyo) 64:442–450. https://doi.org/10.2176/jns-nmc.2024-0105
24. Nakasu S, Deguchi S, Mitsuya K et al (2025) Prognostic implication of CDKN2A/B homozygous deletion on histological grades in isocitrate dehydrogenase-mutant astrocytomas: a systematic review and meta-analysis. Neuro-Oncol Adv 7:vdaf171. https://doi.org/10.1093/noajnl/vdaf171
25. Otsuji R, Hata N, Yamamoto H et al (2024) Hemizygous deletion of CDKN2A/B with p16 immuno-negative and methylthioadenosine phosphorylase retention predicts poor prognosis in IDH-mutant adult glioma Neurooncol Adv. 6:vdae069. https://doi.org/10.1093/noajnl/vdae069/7667045
26. Purkait S, Jha P, Sharma MC et al (2013) CDKN2A deletion in pediatric versus adult glioblastomas and predictive value of p16 immunohistochemistry. Neuropathology 33:405–412. https://doi.org/10.1111/neup.12014
27. Scmidt EE, Ichimura K, Messerie KR et al (1997) Infrequent methylation of CDKN2A(MTS1p16) and rare mutation of both CDKN2A and CDKN2B(MTS2Ip15) in primary astrocytic tumours. Br J Caner 75:2–8. https://doi.org/10.1038/bjc.1997.2
28. Shirahata M, Ono T, Stichel D et al (2018) Novel, improved grading system(s) for IDH-mutant astrocytic gliomas. Acta Neuropathol 136:153–166. https://doi.org/10.1007/s00401-018-1849-4
29. Spiliopoulou P, Yang SYC, Bruce JP et al (2022) All is not lost: learning from 9p21 loss in cancer. Trends Immunol 43:379–390. https://doi.org/10.1016/j.it.2022.03.003
30. Tauziède-Espariat A, Rousseau A, Basset L et al (2025) A comparison of CDKN2A status in gliomas using different techniques: the loss of p16 as a surrogate marker. J Neuropathol Exp Neurol 84:847–854. https://doi.org/10.1093/jnen/nlaf062
31. Wang J, Lan Y, Qi HY et al (2025) Comparison of fluorescence in situ hybridization, next-generation sequencing, and DNA methylation microarray for copy number variation assessment in gliomas. Lab Invest 105:104168. https://doi.org/10.1016/j.labinv.2025.104168
32. Wei Y, Royston P, Tierney JF, Parmar MK (2015) Meta-analysis of time-to-event outcomes from randomized trials using restricted mean survival time: application to individual participant data. Stat Med 34:2881–2898. https://doi.org/10.1002/sim.6556
33. Xi S, Huang Q, Zeng J (2024) A novel grading system combining histological grade and CDKN2A homozygous and hemizygous deletion to predict prognosis in IDH-mutant astrocytoma. J Neuropathol Exp Neurol 83:125–130. https://doi.org/10.1093/jnen/nlad112
34. Yang RR, Shi ZF, Zhang ZY et al (2020) IDH mutant lower grade (WHO grades II/III) astrocytomas can be stratified for risk by

CDKN2A, CDK4 and PDGFRA copy number alterations. Brain Pathol 30:541–553. https://doi.org/10.1111/bpa.12801
35. Yokoda RT, Cobb WS, Yong RL et al (2023) *CDKN2A* mutations have equivalent prognostic significance to homozygous deletion in IDH-mutant astrocytoma. J Neuropathol Exp Neurol 82:845–852. https://doi.org/10.1093/jnen/nlad063
36. Yuile A, Satgunaseelan L, Alexander KL et al (2025) Clinical outcomes and management of *CDKN2A/B* homozygously deleted IDH-mutant astrocytomas—a cohort study and patterns of care survey. Neuro-Oncol Pract 12:787–796. https://doi.org/10.1093/nop/npaf045
37. Zhao L, Claggett B, Tian L et al (2016) On the restricted mean survival time curve in survival analysis. Biometrics 72:215–221. https://doi.org/10.1111/biom.12384
38. Zhao R, Choi BY, Lee MH et al (2016) Implications of genetic and epigenetic alterations of *CDKN2A* (p16(INK4a)) in cancer. EBioMedicine 8:30–39. https://doi.org/10.1016/j.ebiom.2016.04.017
39. Zschernack V, Andreiuolo F, Dorner E et al (2024) P16 immunohistochemistry as a screening tool for homozygous *CDKN2A* deletions in CNS tumors. Am J Surg Pathol 48:46–53. https://doi.org/10.1097/PAS.0000000000002148