Original Article

Segmental chromosome aberrations as a prognostic factor of neuroblastoma: a meta-analysis and systematic review

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Background: Segmental chromosome aberrations, defined as presence of aberrations, deletion, or imbalance in the chromosomal arms, have long been considered as a predictor of poor prognosis of patients with neuroblastoma. The objective of this meta-analysis is to quantitively analyze the hazard ratios (HRs) of different whole or segmental chromosome aberrations for overall survival (OS) rate or event-free survival (EFS) rate of patients with neuroblastoma.

Methods: Relevant studies about chromosome, neuroblastoma, predictor, prognosis, and survival published from the inception to April 2023 in the databases of PubMed, Embase, and Web of Science were searched, screened, and reviewed. The risk of bias of included articles was assessed using the Quality In Prognosis Studies tool. Basic characteristics, HRs of long term (>3 years) EFS and OS with 95% confidence intervals (CIs) of included articles were extracted. A random effects model of DerSimonian-Laird was used to analyze the extracted HRs. For studies that did not report HRs, narrative synthesis was used for summarization.

Results: There were 34 (including 14,356 patients) in 844 searched studies finally included for narrative and quantitative analysis. There were 24 articles rated as low risk of bias and 10 articles rated as moderate. Although the results were inconsistent, the pooled effect of HR for *1p* loss was 4.46 (1.88–10.59) for EFS and 2.29 (1.26–4.15) for OS; the pooled effect of HR for *17q* gain was 4.81 (3.29–7.04) for EFS and 3.98 (2.11–7.54) for OS; the pooled effect of HR for *11q* loss was 2.54 (2.32–3.73) for OS. Results of *1p36* loss, *1p22* loss, *11q23* loss, *11q13-q14* gain, *1q* gain, *1q22* gain, *2p* gain, *3p* loss, *4p* loss, *14q* loss, *14q32* loss, and other segmental chromosome aberrations were also summarized.

Conclusions: *1p* loss, *11q* loss, and *17q* gain were identified as significant independent predictors for long-term OS and EFS of patients with neuroblastoma.

Keywords: Segmental chromosome aberrations; neuroblastoma; prognostic factors; survival

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Introduction

Neuroblastoma is a developing tissue disease, in which the cells originate from precursor cells incompletely developed from neuro crest tissues (1). Arising in the sympathetic nervous system, usually in the adrenal medulla (40%) or other abdominal site (25%), it can also occur in the pelvis (5%), neck (15%), and bone cavity (5%) as mass lesion (2-4). As expected with an embryonal tumor, it is one of

the most common pediatric tumors in children, with a median age of diagnosis of 17 months and 37% of cases are diagnosed during infancy (5,6). Neuroblastoma accounts for 8–10% of all childhood malignancies (8.7 cases per million for all; 10.2 cases per million for children under 15 years old) and 15% of childhood tumor deaths (2,7,8). The etiology of neuroblastoma is still unconfirmed but several preconceptual or gestational factors have been suggested to play a significant role, including gestational diabetes, exposure to toxins, viruses, or drugs, and deficiency of folic acid (9-12).

The clinical and phenotypic variability of neuroblastoma is remarkable, ranging from asymptomatic masses with a favorable outcome to aggressive malignant tumors with local invasion or/and widespread dissemination, which is known as high-risk neuroblastoma (2,13). The diversity in the clinical behaviors of this tumor is associated with numerous clinical [such as age and International Neuroblastoma Staging System (INSS)], biological (such as tumor dormancy), and genetic features (such as *MYCN* gene amplification and ferroptosis-related gene signature), which are used to stratify patients into three risk subgroups with low, intermediate, and high risks of death (with high, intermediate, and low expected survival rates, respectively) (13-16). The International Society of Pediatric Oncology Europe Neuroblastoma Group uses age at diagnosis, *MYCN* gene amplification, and surgical factors by imaging for risk group assignment (17). The Children's Oncology Group uses postsurgical tumor stage, histology by Shimada method, and DNA ploidy except for common age and *MYCN* gene amplification for risk group assignment (18). Furthermore, the International Neuroblastoma Risk Group (INRG) has identified grade of tumor differentiation and chromosome 11q (long arm of chromosome 11) status as new predictors for risk assessment (13).

Since last century, segmental chromosome aberrations have been demonstrated to be associated with poor survival outcome of neuroblastoma. A segmental chromosome aberration is defined as either presence of aberrations in the corresponding chromosomal arms identified by fluorescent in situ hybridization (FISH) method, or deletion or imbalance determined by loss of heterozygosity (LOH) analysis (13,19). The aberrations can be in whole short/long arm (p/q), or a specific part of arms. Loss of *1p*, *3p*, *4p*, and *11q* is associated with poor prognosis of neuroblastoma, whereas gain of *1q*, *2p*, *12q*, and *17q* is related to poor outcomes (20-25). Recent studies have shown that instead of whole chromosome arm loss or gain, the loss or gain of specific parts of chromosomes is of higher prognostic value (26). Loss of *1p36*, *1p22*, *6q27*, and *11q23* predicts poor overall survival (OS) and event-free survival (EFS) of patients with neuroblastoma, as does gain of *1q22*, *2p22*, and *12q24* (21,27-29).

There has been controversy associated with the prognostic significance of segmental chromosome aberrations. Some studies could not find any prognostic significance of *1p* deletion, *11q* deletion, and *17q* gain for neuroblastoma (30-32). The reason for this controversy is still unclear. Lim *et al.* speculated that the chemotherapy for patients with segmental chromosome aberrations varied among studies, which likely caused a difference in survival outcomes (30). To solve the controversy, a meta-analysis is needed to quantitatively analyze the effect of segmental chromosome aberrations on predicting survival of patients with neuroblastoma, which has not been performed before.

The objective of this meta-analysis is to analyze the hazard ratios (HRs) of different whole or segmental chromosome aberrations for OS or EFS rate of patients with neuroblastoma, and further provide useful evidence for clinical decision and recommendation. We present this article in accordance with the PRISMA reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-200/rc).

Highlight box

Key findings

- *1p* loss, *11q* loss, and *17q* gain were significant independent predictors for long-term overall survival (OS) and event-free survival (EFS) of patients with neuroblastoma.

What is known and what is new?

- Since last century, segmental chromosome aberrations have been demonstrated to be associated with poor survival outcomes of neuroblastoma. Recent studies have shown that instead of whole chromosome arm loss or gain, the loss or gain of specific parts of chromosomes is of higher prognostic value. However, there has been no meta-analysis quantitatively analyzing the effect of these whole or segmental chromosome aberrations on predicting survival of patients with neuroblastoma.
- This article systematically analyzes the hazard ratios of different whole or segmental chromosome aberrations for OS rate or EFS rate of patients with neuroblastoma.

What is the implication, and what should change now?

- Future studies should report comprehensive and detailed statistical results and focus on special genes on these chromosomes.

Methods

Inclusion criteria

Population: patients diagnosed with neuroblastoma for the first time regardless of stages, tumor sites, *MYCN* gene amplification, and other clinical behaviors.

Prognostic factors: segmental chromosome aberrations, defined as loss or gain of whole arms or specific parts of autosomes and sex autosomes. Studies focusing on numerical chromosome aberrations or other genetic factors are excluded.

Outcomes: long term (>3 years) EFS (including relapse-free survival and progression-free survival) and OS.

Study type: original articles focusing on prognosis analysis of patients. Reviews and meta-analyses were excluded. Studies focusing on neuroblastoma cells or other animals were also excluded. Only English-language articles were accepted.

Searching strategy

The databases of PubMed, Embase, and Web of Science were searched for eligible original studies published from inception to April 2023. The keywords searched were chromosome, neuroblastoma, predictor, prognosis, and survival (Appendix 1). All searched records were imported into Endnote 20 (Clarivate, Philadelphia, PN, USA), where duplicates were removed. Thereafter, records with irrelevant titles and abstracts were removed, and the full texts of the remaining articles were obtained and reviewed. Illegible records were removed after full text review and reasons for exclusion were recorded in a flow diagram of study selection. To improve comprehensiveness, the reference lists of the included full text records were further screened for additional eligible records.

Data extraction

Basic characteristics of included articles were extracted: first name of first author, publication year, country, total sample size, mean or median age of patients at first diagnosis and percentage of female patients. Both adjusted and unadjusted HRs of long term (>3 years) EFS and OS with 95% confidence intervals (CIs) were extracted for quantitative synthesis. If HRs were not provided, brief descriptions of results were also collected.

Quality evaluation

The risk of bias of the included articles was evaluated using the Quality In Prognosis Studies tool (33). This tool is composed of 6 bias domains:

- Study participation: assess the risk of selection bias by participation rate, source population statement, baseline sample description, recruitment details, sampling description, and selection criteria.
- Study attribution: assess the risk of attribution bias by response rate, attempt to collect information on patients who dropped out, description of loss to follow up, and outcome and prognostic factor information on patients who dropped out.
- Prognostic factor measurement: assess the risk of measurement bias related to prognostic factors by definition, measurement description, measurement consistency, blindness, continuity or cut-off of variables, and methods to deal with missing data.
- Outcome measurement: assess the risk of measurement bias related to outcomes by definition, measurement description, and consistency.
- Study confounding: assess the risk of confounding bias by inclusion of important confounding factors, definition, consistency of measurement, and appropriate accounting for confounding factors in study design and analysis.
- Statistical analysis and reporting: assess the risk of reporting bias by analytical strategy description, model appropriateness, model adequacy, and reporting of results.

All six domains above are rated as high, moderate, or low risk of bias. If all domains are rated as low or only 1 domain is rated as moderate with others rated as low, the article is rated as low risk of bias. If 1–2 domains are rated as high or 2–3 domains are rated as moderate, the article is rated as moderate risk of bias. If more than 2 domains are rated as high or more than 3 domains are rated as moderate, the article is rated as high risk of bias.

Statistical analysis

For articles that provided HRs of EFS or OS, a random effect model of DerSimonian-Laird was used to analyze the pooled effect (34). R language with Rstudio environment (R Foundation for Statistical Computing, Vienna, Austria) was used to perform meta-analysis and the main package was "metafor". Tau^2 test and I^2 level were used to measure heterogeneity of included articles. Tau^2 represents the between-study variance whereas I^2 represents the proportion of total variation across studies truly due to heterogeneity

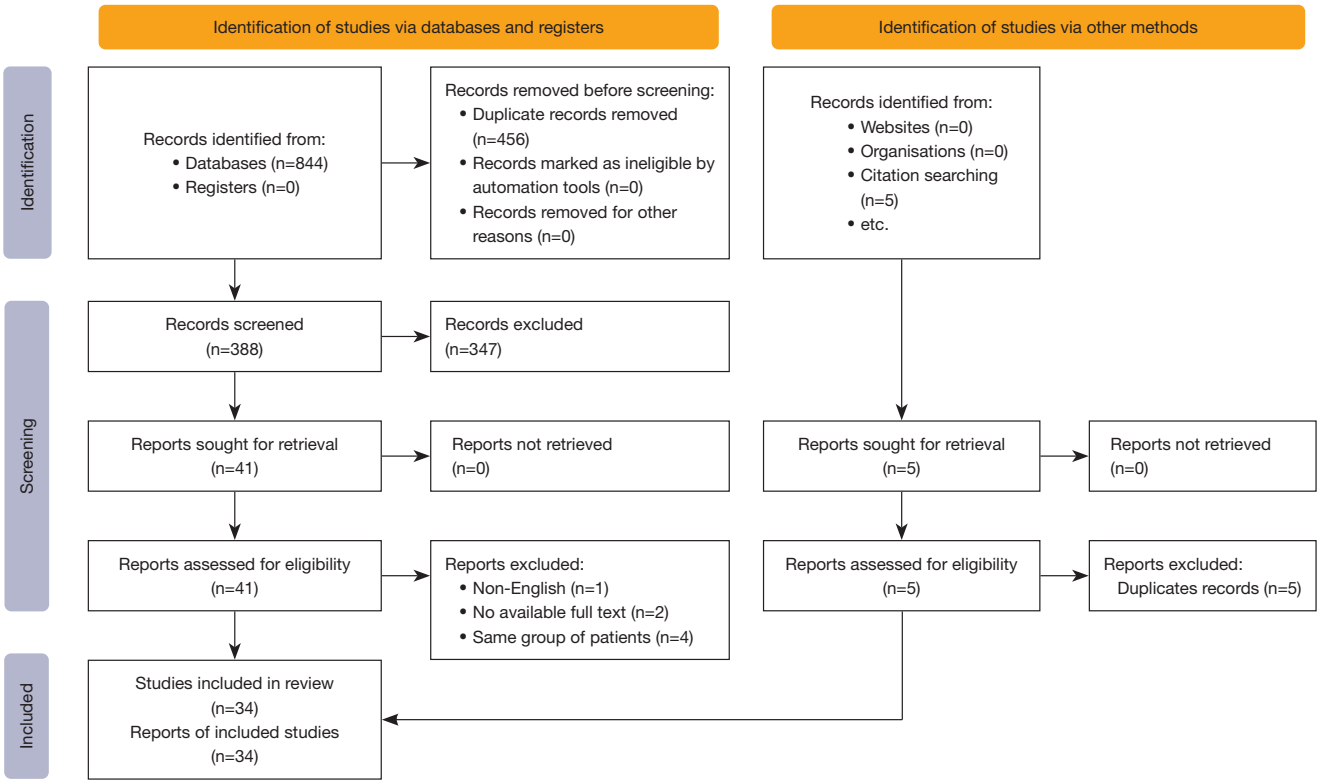

Figure 1 Flow diagram of study selection.

rather than chance. When a P value of Tau^2 test was <0.1 and I^2 level was >50%, the level of heterogeneity among the included studies was considered high.

For articles lacking reporting of HRs of EFS and OS, narrative synthesis was used for summarization.

Results

Study selection

The database search yielded 844 records, with 290 from PubMed, 229 from Embase, and 325 from Web of Science (*Figure 1*). A total of 456 duplicates were removed and titles and abstracts of the remaining 388 records were screened. A further 347 records with irrelevant titles and abstracts are removed and the full texts of the remaining 41 records were obtained and reviewed. A total of seven records were removed: one for non-English written language, two for no available full text, and four for same group of patients. Additionally, five articles were found through screening reference lists of included records. A total of 34 records were included for further qualitive, narrative, and quantitative analysis.

Study characteristics and quality

The basic characteristics and results of risk assessment are summarized in *Table 1*. The 34 included articles were published from 1988 to 2022. A total of 21 studies were conducted in Europe, 5 were conducted in Asia, 1 was conducted in Africa, 5 were conducted in America, and 2 were conducted across multiple countries. In total, the 34 articles included 14,356 patients and the sample size ranged from 23 to 7,251. The mean or median age of patients at first diagnosis ranged from 12 to 34.8 months. The percentage of female patients ranged from 41.4% to 90%.

A total of 24 articles were rated as low risk of bias. The other 10 articles were rated as moderate risk of bias due to either insufficient description of study participants or insufficient consideration of confounding factors. No article was rated as high risk of bias, so all articles were included for further narrative and quantitative analysis.

Narrative and quantitative analysis

1p loss, *1p36* loss, and *1p22* loss

A total of 25 articles reported inconsistent results of *1p*

Table 1 Characteristics of studies

Author	Publication year	Country	Total sample	Mean/median age at diagnosis (months)	Female (%)	Risk level
Christiansen *et al.* (20)	1988	Germany	28	26	46.4	Moderate
Caron *et al.* (35)	1995	Netherlands	55	–	–	Low
Christiansen *et al.* (36)	1995	Germany	377	–	–	Moderate
Caron *et al.* (22)	1996	Netherlands	89	–	–	Low
Takeda *et al.* (37)	1996	Japan	154	–	–	Low
Schleiermacher *et al.* (38)	1996	France	82	20	–	Moderate
Rubie *et al.* (39)	1997	France	91	12	48.4	Low
Lastowska *et al.* (25)	1997	UK	45	–	90	Moderate
Hesseling *et al.* (40)	1999	South Africa	48	18	52.6	Moderate
Maris *et al.* (28)	2000	USA	238	–	–	Low
Bown *et al.* (24)	2001	UK	104	24	–	Low
Mora *et al.* (27)	2002	USA	84	–	52.4	Low
Attiyeh *et al.* (41)	2005	USA	915	–	–	Low
Vandesompele *et al.* (23)	2005	Belgium	231	19	–	Low
Henrich *et al.* (42)	2006	Germany	102	–	–	Low
Burgues *et al.* (43)	2006	Spain	182	20.5	–	Low
Mosse *et al.* (21)	2007	USA	82	–	–	Low
Janoueix-Lerosey *et al.* (26)	2009	France	222	–	–	Low
Pezzolo *et al.* (44)	2009	Italy	23	–	–	Moderate
Jeison *et al.* (45)	2010	Israel	177	34.8	42.4	Low
Ramani *et al.* (46)	2012	UK	69	–	–	Low
Schleiermacher *et al.* (47)	2012	France	505	–	–	Low
Dungwa *et al.* (48)	2012	UK	98	–	–	Low
Verly *et al.* (31)	2018	Netherlands	301	23	42.5	Low
Szewczyk *et al.* (49)	2019	Poland	105	–	–	Low
Parodi *et al.* (50)	2019	Italy	174	–	41.4	Low
Twist *et al.* (32)	2019	USA	404	–	–	Moderate
Campbell *et al.* (51)	2019	Multiple countries	7,251	–	–	Moderate
Qin *et al.* (52)	2019	China	792	–	–	Low
Ognibene *et al.* (29)	2020	Italy	747	–	–	Moderate
Ambros *et al.* (53)	2020	Multiple countries	317	–	–	Low
Lim *et al.* (30)	2020	Korea	173	30	48.6	Low
Salim *et al.* (54)	2021	UK	117	–	–	Moderate
Yue *et al.* (55)	2022	China	154	43	43.5	Low

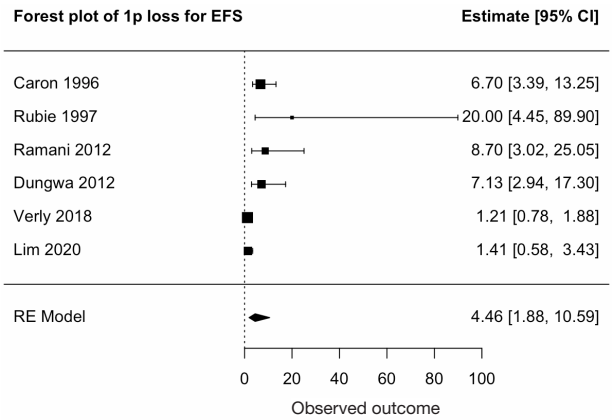

Figure 2 Forest plots of 1p loss. EFS, event-free survival; CI, confidence interval; RE, random effects.

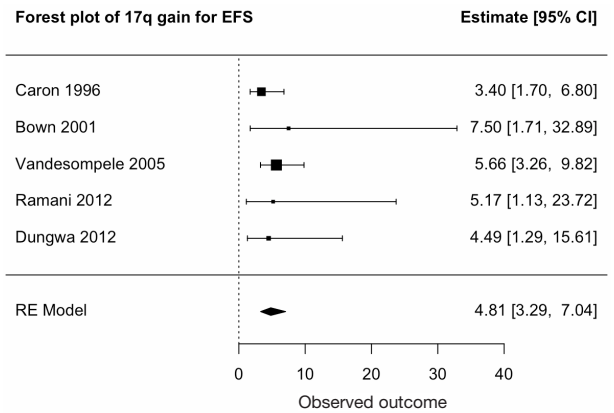

Figure 3 Forest plots of 17q gain. EFS, event-free survival; CI, confidence interval; RE, random effects.

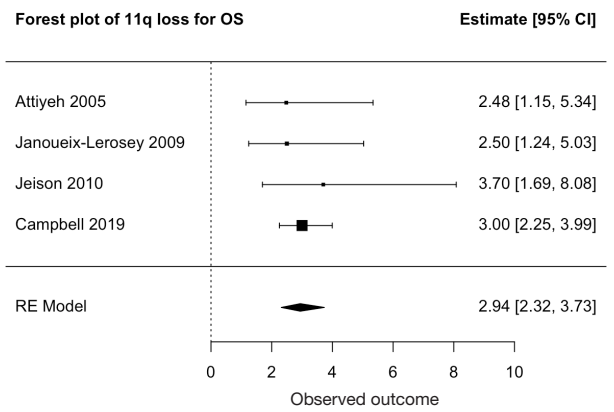

Figure 4 Forest plots of 11q loss. OS, overall survival; CI, confidence interval; RE, random-effects.

loss. As shown in *Figure 2*, the pooled effect of HR was 4.46 (95% CI: 1.88–10.59; six studies) for EFS with high heterogeneity (I^2=85.34%) and 2.29 (95% CI: 1.26–4.15; eight studies) for OS with high heterogeneity (I^2=81.90%). However, Lastowska *et al.*, Ambros *et al.*, Jeison *et al.*, and Twist *et al.* reported non-significance of *1p* loss for EFS, whereas Takeda *et al.* reported significance (25,32,37,45,53). Hesseling *et al.*, Vandesompele *et al.*, Burgues *et al.*, Mosse *et al.*, Jeison *et al.*, Schleiermacher *et al.*, Ambros *et al.*, and Salim *et al.* reported non-significance of *1p* loss for OS, whereas Christiansen *et al.*, Caron *et al.*, and Schleiermacher *et al.* reported significance (20-23,36,38,40,43,45,47,53,54).

A total of 5 articles reported inconsistent results of *1p36* loss. For OS, Mora *et al.* and Maris *et al.* reported that it was not a significant predictor whereas Attiyeh *et al.* reported its HR of 2.92 with 95% CI of 1.48–5.76 in multivariate analysis (27,28,41). For EFS, Maris *et al.* reported its HR of 1.90 with 95% CI of 1.21–2.97 in multivariate analysis, whereas Pezzolo *et al.* and Yue *et al.* reported non-significance in multivariate analysis with significance in univariate analysis (28,44,55).

Mora *et al.* also reported that *1p22* loss was not a significant predictor for OS (27).

17q gain

A total of 15 articles reported inconsistent results of *17q* gain. As shown in *Figure 3*, the pooled effect of HR was 4.81 (95% CI: 3.29–7.04; five studies) for EFS without heterogeneity (I^2=0) and 3.98 (95% CI: 2.11–7.54; three studies) for OS without heterogeneity (I^2=0). However, Jeison *et al.*, Ambros *et al.*, and Lim *et al.* reported non-significance of *17q* gain for EFS, whereas Lastowska *et al.* reported significance (25,30,45,53). Mora *et al.*, Mosse *et al.*, Janoueix-Lerosey *et al.*, Jeison *et al.*, Schleiermacher *et al.*, Lim *et al.*, and Salim *et al.* all reported non-significance of *17q* gain for OS, whereas Ambros *et al.* reported significance (21,26,27,30,45,47,53,54).

11q loss, *11q23* loss, and *11q13-q14* gain

A total of 12 articles reported inconsistent results of *11q* loss. As shown in *Figure 4*, the pooled effect of HR was 2.94 (95% CI: 2.32–3.73; four studies) for OS without heterogeneity (I^2=0). However, Lim *et al.*, Salim *et al.*, Schleiermacher *et al.*, and Mosse *et al.* all reported non-significance of *11q* loss for OS, whereas Ambros *et al.* reported significance (21,30,47,53,54). For EFS, Caron *et al.*, Takeda *et al.*, Amros *et al.*, and Lim *et al.* all reported

non-significance of *11q* loss for EFS, whereas Twist *et al.* reported significance (22,30,32,37,53).

A total of 4 studies reported inconsistent results of *11q23* loss. For OS, Mora *et al.* and Attiyeh *et al.* reported that it was not a significant predictor, whereas Mosse *et al.* reported it as a significant predictor with P<0.0001 (21,27,41). For EFS, Yue *et al.* reported that it was not a significant predictor for all patients, but it was a significant predictor for *MYCN* gene nonamplified patients with HR =1.774 (95% CI: 1.007–3.126) (55).

Mosse *et al.* also reported that *11q13-q14* gain was a significant predictor for EFS (21).

1q gain and *1q22* gain

A total of 3 studies reported inconsistent results of *1q* gain. For OS, Ambros *et al.* reported it as a significant predictor with P=0.002, whereas Vandesompele *et al.* and Janoueix-Lerosey *et al.* reported that it was not significant in multivariate analysis (23,26,53). Ambros *et al.* also reported non-significance in multivariate analysis of EFS (53).

Pezzolo *et al.* reported that *1q22* gain was not a significant predictor for OS (44).

2p gain

A total of 3 studies reported inconsistent results of *2p* gain. Janoueix-Lerosey *et al.* and Szewczyk *et al.* reported its non-significance for OS, whereas Ambros *et al.* reported that it was a significant predictor both for OS and EFS in univariate analysis (26,49,53).

3p loss, *4p* loss, *14q* loss, and *14q32* loss

The results for these segmental chromosome aberrations were consistent. Ambros *et al.*, Vandesompele *et al.*, and Janoueix-Lerosey *et al.* all reported non-significance of *3p* loss for OS and Ambros *et al.* also reported non-significance of *3p* loss for EFS (23,26,53). Janoueix-Lerosey *et al.* and Ambros *et al.* both reported non-significance of *4p* loss for OS, and Ambros *et al.* and Caron *et al.* both reported non-significance of *4p* loss for EFS (22,26,53). Caron *et al.* and Takeda *et al.* both reported non-significance of *14q* loss for EFS and Mora *et al.* reported non-significance of *14q32* loss for OS (22,27,37).

Others

Mora *et al.* reported that both *19q13* loss and *9p21* loss were not significant predictors for OS (27). Mosse *et al.* reported that *3q* gain, *6p* gain, *10q* gain, and *12q* gain were all significant predictors for EFS in univariate analysis, whereas only *12q24* gain was a significant predictor for EFS in multivariate analysis (21). Pezzolo *et al.* reported significance of *7p11.2p22* gain for EFS (44). Parodi *et al.* reported non-significance of chromosome X for OS (50). Qin *et al.* reported significance of *11p14* gain for OS (52). Ognibene *et al.* reported that *6q27* was responsible for poor OS (29).

Discussion

A total of 34 articles were included for analysis and the pooled effects suggested that *1p* loss, *11q* loss, and *17q* gain were significant independent predictors for long-term OS and EFS of patients with neuroblastoma. However, the evidence level of these results is still doubtful.

Although 25 articles reported *1p* loss, the number of studies reporting HRs of OS and EFS was still less than 10, which means that test of publication bias and leave one out sensitive analysis were not applicable in this case. Moreover, quite a few of the included studies did not report HRs of *1p* loss in multivariate analysis because of non-significance in univariate analysis, making this pooled effect biased. Besides, the heterogeneity of pooled effects was very high (>80%), making the credibility weaker. Similar to *1p* loss but without heterogeneity, quite a few studies did not report HRs of *17q* gain and *11q* loss, making the results biased.

As for other segmental chromosome aberrations reported in at least 3 articles, only the results of *3p* loss, *4p* loss, *14q* loss, and *14q32* loss were consistent with non-significance. The results of *1p36* loss, *11q23* loss, *1q* gain, and *2q* gain were inconsistent and more articles reported non-significance. With regard to the remaining chromosome aberrations reported only in 1 or 2 studies, more evidence is needed for synthesis.

The potential mechanism of action of segmental chromosome aberrations remained unknown, yet articles reporting on it indicated that it was not related to *MYCN* gene amplification (26,30). Stigliani *et al.* reported that neuroblastoma with segmental chromosome aberrations tend to accumulate additional genetic instability so the coexistence of several segmental chromosome aberrations should be considered (56). Besides, Szewczyk *et al.* speculated that *2p* gain causes a partial trisomy of *2p*, which contains several genes involved in carcinogenesis such as *ADAM17*, *ALK*, and *BCL11A* (49). Ognibene *et al.* also reported that *SFT2D1*, *RPS6KA2*, and *FGFR1OP* genes on *6q27* were responsible for poor prognosis of patients with

high-risk neuroblastoma with *6q27* loss (29). Therefore, specific genes on altered chromosomes can act as surrogate markers for segmental chromosome aberrations and will confer an extra edge to the selection (57). Future studies should focus on the relationship between specific genes, segmental chromosome aberrations, and prognosis of patients with neuroblastoma to further research on the potential mechanism.

This meta-analysis has some limitations as mentioned before. First, the number of eligible articles for quantitative synthesis is too small to conduct test of publication bias and leave one out sensitive analysis. Second, quite a few studies reporting non-significance provided HRs, making the synthesized result biased. Third, all of the included studies were English-language and none of the non-English datasets were searched, leading to language bias. Therefore, the evidence level of these results was not that high.

Conclusions

In conclusion, *1p* loss, *11q* loss, and *17q* gain were shown to be significant independent predictors for long-term OS and EFS of patients with neuroblastoma. Future studies should report comprehensive and detailed statistical results and focus on special genes on these chromosomes.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-200/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-200/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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