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ABSTRACT

Background

Brain metastases (BM) in patients with advanced and metastatic non-small cell lung cancer (NSCLC) are linked with poor prognosis. Identifying genomic alterations associated with BM development could influence screening and determine targeted treatment. We aimed to establish prevalence and incidence in these groups, stratified by genomic alterations.

Patients and Methods

A PRISMA-compliant systematic review and meta-analysis was conducted (PROSPERO ID CRD42022315915). Articles published in MEDLINE, EMBASE, and Cochrane Library between January 2000-May 2022 were included. Prevalence at diagnosis, and incidence of new BM per year were obtained, including patients with *EGFR, ALK, KRAS*, and other alterations. Pooled incidence rates were calculated using random effects models.

Results

Sixty-four unique articles were included (24,784 NSCLC patients with prevalence data from forty-five studies and 9,058 NSCLC patients with incidence data from forty studies). Pooled BM prevalence at diagnosis was 28.6% (45 studies, 95% Confidence Interval [CI] 26.1-31.0), and highest in patients that are *ALK*-positive (34.9%) or with *RET*-translocations (32.2%). With a median follow-up of 24 months, per-year incidence of new BM was 0.13 in the wild-type group (14 studies, 95% CI 0.11-0.16). Incidence was 0.16 in the *EGFR* group (16 studies, 95% CI 0.11-0.21), 0.17 in the *ALK* group (5 studies, 95% CI 0.10-0.27), 0.10 in the *KRAS* group (4 studies, 95% CI 0.06-0.17), 0.13 in the *ROS1* group (3 studies, 95% CI 0.06-0.28), and 0.12 in the *RET* group (2 studies, 95% CI 0.08-0.17).

Conclusions

Comprehensive meta-analysis indicates a higher prevalence and incidence of BM in patients with certain targetable genomic alterations. This supports brain imaging at staging and follow-up, and the need for targeted therapies with brain penetrance.

INTRODUCTION

Lung cancer is a major global health problem, with an estimated 2 million new cases every year and 1.8 million deaths.[1] Non-small cell lung cancer (NSCLC) is the commonest form and accounts for 85% of all lung cancers.[2] Advanced (Stage III) and metastatic (Stage IV) NSCLC confer the worst prognosis, with 5-year survival rates of 15% and 5% respectively.[3] The survival is improving due to a combination of novel targeted agents, earlier diagnosis, and other treatment advances such as immunotherapy.[4] Recent trials have demonstrated improved overall survival (OS) with targeted therapies for tumors carrying specific genomic alterations, such as *EGFR*[5] and *ALK.*[6,7]

Up to 60% of patients with NSCLC are expected to have central nervous system (CNS) involvement at some point during their disease.[8] Development of brain metastases (BM) specifically in NSCLC is associated with reduced OS, progression-free survival (PFS), and quality of life,[9,10] although earlier detection seems to improve survival.[10] Screening programmes to detect asymptomatic BM and the use of prophylactic cranial irradiation (PCI) to reduce the risk of BM development remain controversial.[11,12] There is a knowledge gap around the prevalence of BM, the rate at which they develop, and the factors that drive the process.[13] Although the discovery of genomic alterations in NSCLC has facilitated the development of targeted agents, the impact of these alterations (such as *EGFR*, *ALK, KRAS, ROS1, RET*, and others) on BM development remains mostly unclear.

A systematic review and meta-analysis of the incidence and prevalence of BM in NSCLC both overall and stratified by genomic alterations is valuable. It would help clinicians understand the full burden of disease, quantify the potential benefits of BM screening programmes and to individualize treatment and monitoring in any subgroups at higher risk. The following questions were therefore addressed in this review: 1. In patients with advanced and metastatic NSCLC, what is the prevalence of BM at diagnosis and the incidence of new BM per year, and 2. Do these figures differ by the presence of the most common genomic alterations?

MATERIAL AND METHODS

Search strategy and selection criteria

We conducted a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] The review was registered in PROSPERO (CRD42022315915) and the protocol changed once to allow a combined rate of BM among NSCLC populations at the end of follow-up to be calculated.

We searched Medline, Embase, and the Cochrane database of systematic reviews for full-text articles published in English, between the publication date 1st January 2000 and 30th May 2022. The date of last search was 30th April, 2022. Search terms used a combination of the words 'lung', 'met', and 'incidence' (Supplementary Table 1, 2, and 3). The Population, Intervention, Comparator, Outcome, Study Design (PICOS) criteria was used (Supplementary Table 4). We included studies of adults (≥16 years) with either advanced (Stage III) or metastatic (Stage IV) NSCLC that reported either the prevalence of BM at diagnosis, incidence, or both. We excluded studies that were conference abstracts, and studies published before January 2000 (to exclude the pre-MRI era as this greatly affects BM detection).[15] We excluded studies with selective populations (including studies of only BM), and if stage specific data was unavailable. For studies that were randomized control trials (RCTs), we excluded treatment arms if they included PCI as an intervention, as PCI is currently not standard of care and could affect BM incidence.

Three reviewers (CSG, MAM, GER) independently screened titles, abstracts and full-text to include articles. If reviewers failed to reach consensus, a pair of senior authors, one a trained medical statistician (DH, RZ) made a final determination.

Data extraction

Data extraction was completed in full and in duplicate by at least two authors per paper. The following data were gathered about included studies: year published, journal, type of

study (RCT and observational), and stages of NSCLC included (Stage III, Stage IV, or mixed). If the study was an RCT, the intervention and type of treatment were recorded (e.g. Tyrosine Kinase Inhibitors [TKI], chemotherapy, PCI).

Numerical data extracted from each study: total population with NSCLC, number of patients with BM at diagnosis, prevalence at diagnosis, median follow-up time (months), total number of patients without BM who had follow up, total number of patients developing BM, overall incidence of BM, and incidence per year of patient follow up. Median time to development of BM from NSCLC diagnosis was extracted if available. It was specifically noted if a screening programme to detect BM was used during follow-up.

Quality assessment

Retrospective studies were classified according to the Newcastle Ottawa Scale,[16] and RCTs were assessed according to the Cochrane Risk of Bias 2.0 tool.[17] For studies that were *post-hoc* analyses of prior RCT data, we assessed the original trial publication from which data was extracted.

Definitions

A study was defined as a 'mixed' cohort if it included both Stage III and Stage IV patients together – this was often studies that described 'advanced' lung cancer without specifying stage. Studies were recorded as having a screening program in place to detect BM during follow-up if they specified the time when patients were scanned regardless of symptoms (which were often as part of standardized imaging protocols). Annual incidence rates were calculated by dividing the number of patients who developed BM during follow-up/number of patients without BM at start of study period, divided by the length of that follow up period in months then multiplying by 12.

Statistical analysis

For the meta-analysis, we used a random effects model for pooled proportions estimates for prevalence at diagnosis, and meta-analysis of single incidence rates for per-year incidence.[18,19] This was repeated for each molecular subgroup, with two or more included studies required to perform meta-analysis. We generated forest plots for incidence based on a random intercept generalized linear mixed model. For each random effects model, we tested heterogeneity using the maximum restricted likelihood estimator. Prevalence was calculated using pooled proportions methods using the inverse variance method. Total heterogeneity and I^2 characteristics were calculated. Publication bias was evaluated and presented as funnel plots.

Sensitivity analysis was performed to assess the effect of the following variables in our analysis: Screening programmes, high risk of bias, and Stage. For the *ALK*-positive subgroup, since it is known that second and third generation TKIs such as Alectinib, Brigatinib, and Lorlatinib significantly reduce BM incidence[7,20] we analyzed the data for all patients, then excluding those receiving such agents.

All statistical analysis was supervized by a senior academic statistician (DMH). Data analysis of descriptive statistics was performed using SPSS (Version 27; IBM; Armonk; NY; USA). R statistics (Rstudio Version 4.0.1) was used to perform meta-analysis, and create figures, forest, and funnel plots (ggplot2 and meta packages).

RESULTS

Systematic Review and Characteristics

After full-text assessment, 132 studies were assessed as possibly suitable for inclusion. An additional 70 studies were then excluded (Supplementary Table 5). An additional two studies were identified by hand searching, resulting in 64 total studies being included in the analysis after applying inclusion and exclusion criteria (Figure 1). In total, six studies were RCTs, [21-27] four studies were *post-hoc* analyses of RCTs,[20,28-31] and 54 were observational studies. In total, forty-five studies included prevalence data, and forty studies included incidence data. Of the forty-five studies with prevalence data, twenty one included incidence rates, giving 64 unique studies in total.

Baseline characteristics

The baseline characteristics of included studies are shown in detail (Supplementary Table 6). The median number of patients included per study was 199 (IQR 111-472, range 4-6,545). Of these, 45 studies had brain metastatic status at diagnosis available (24,784 patients), and 40 studies had BM incidence available for patients without BM at presentation (9,058 patients). Included studies used a variety of methods to assay for genomic alterations including FISH, next generation sequencing (NGS), arrays, and/or combinations of these. No studies used liquid biopsies to detect genomic alterations.

Screening and follow-up

Eleven studies (16.9%) reported screening patients for BMs as part of follow-up protocols. Among the 40 studies with incidence data, the median follow-up period was 24 months (IQR 16-36 months).

Prevalence of BM at diagnosis

Forty-five studies including 24,784 patients reported BM prevalence at diagnosis of metastatic NSCLC, with a prevalence of 28.4% (95% CI 26.0-30.9) (Supplementary Table 6). Pooled prevalence among Stage IV studies was 26.8% (95% CI 24.0-29.6). The pooled prevalence for mixed studies containing both Stage III and Stage IV was 33.1% (95% CI 27.3-39.2).

BM prevalence in patients with specific genomic alterations

Pooled prevalence forest plots are shown in Table 1 and Supplementary Figure 1. Pooled prevalence was 29.4% in the *EGFR*-positive group (22 studies, 3990 patients, 95% CI 24.5-34.5), 34.9% in the *ALK*-positive group (9 studies, 782 patients, 95% CI 23.4-47.3), and 30.2% in the *KRAS*-positive group (8 studies, 695 patients, 95% CI 24.4-36.2). Prevalence was 29.4% in the *ROS1*-positive group (3 studies, 141 patients, 95% CI 29.5-34.5), 32.2% in the *RET*-

positive group (3 studies, 203 patients, 95% CI 18.6-47.3), and 28.8% in the wild-type group (9 studies, 14,447 patients, 95% CI 23.7-34.2).

Pooled incidence of BM

The pooled incidence is shown in Table 2 (Supplementary Table 7). Forty studies including 9,058 patients without BM at diagnosis of advanced NSCLC reported cumulative incidence. The pooled incidence per year was 0.11 (95% CI 0.09-0.13) (Supplementary Figures 2 and 3). The pooled incidence per year among Stage IV studies was 0.12 (95% CI 0.09-0.15). The pooled incidence among Stage III studies was 0.11 (95% CI 0.08-0.15).

Pooled incidence stratified by genomic alterations

Pooled incidence plots are shown in Figures 2 and 3 (Supplementary Table 8). Using random effects models, pooled incidence of new BM was 0.16 per-year in the *EGFR*-positive group (16 studies, 2556 patients, 95% CI 0.11-0.21), and 0.12 per-year in the *ALK*-positive group (6 studies, 630 patients, 95% CI 0.07-0.17). When removing patients treated with second or third generation TKIs in the *ALK*-positive cohort, the incidence increased to 0.17 per year (95% CI 0.10-0.27) (Figure 3). Incidence was 0.10 per-year in the *KRAS*-positive group (4 studies, 286 patients, 95% CI 0.06-0.18). One study provided information on types of TKI treatment: 8 patients received no treatment (12.3%), 55 (84.6%) chemotherapy at any point, 2 (3.1%) EGFR-TKI, and 16 on EGFR-TKI at any point in treatment.

Pooled incidence of new BM was 0.13 per-year in the *ROS1*-positive group (3 studies, 117 patients, 95% CI 0.06-0.28), and 0.12 per-year in the *RET*-positive group (2 studies, 113 patients, 95% CI 0.08-0.17). In the *RET*-positive group, one study referenced Multikinase inhibitor treatment that included multiple agents.[32] In one study, 46 (78%) had permetrexed based chemotherapy, 19 (32.3%) vandetanib, 12 (20.3% EGFR TKI), and 13 (22.0%) immunotherapy.[33] In the C-MET exon skipping mutation group, the rate was 0.08 per-year (2 studies, 72 patients, 95% CI 0.06-0.11). Pooled incidence of new BM was 0.13 per-year in the wild-type group (14 studies, 2156 patients, 95% CI 0.11-0.16).

Incidence amongst other genomic subtypes- BRAF, PI3CK, HER-2, FGFR1

As all other genomic subtypes included fewer than 2 studies, their results are presented descriptively (Supplementary Table 9 and Figure 4). Of these, the *HER-2* positive group had the highest per-year incidence rate (0.23). Forty-three percent of the patients in the *HER-2*-group (42 of 98) received *HER-2*-targeted therapy at diagnosis (afatinib, neratinib, ado-trastuzumab emtansine, trastuzumab, and/or dacomitinib).[34]

Combined prevalence and incidence at the end of follow-up period

21 studies including 6425 patients reported both a prevalence and number developing BM at the end of the follow-up period. Among these, the combined incidence and prevalence at the end of the study period – median 2 years - was 55.0% (IQR 42.2-67.8).

Assessment of bias

The assessment of bias for retrospective cohort studies, using the Newcastle-Ottowa Scale, is shown (Supplementary Figure 4). The mean score (out of 9) for all studies was 7.5, and 11 studies were classified as high risk of bias. For the RCTs and post-hoc analysis of RCTs, one study was classified as high risk of bias (Supplementary Figure 5). The funnel plots for each forest plot generated are shown (Supplementary Figure 6).

Sensitivity analysis

The results of the 3-step sensitivity analysis are shown (Supplementary Table 10). There was no difference in the rates of incidence of BM when comparing Stage 3 to Stage 4 NSCLC. Removing the ten retrospective studies and one RCT classified as high risk of bias increased the incidence per year to 0.12 (95% CI 0.10-0.14) from 0.07 (95% CI 0.05-0.11). Studies that actively used a screening programme had no difference in BM incidence compared to studies without a screening programme (0.10, 95% CI 0.07-0.13 vs 0.11, 95% CI 0.09-0.13).

DISCUSSION

This is the first systematic review and meta-analysis to combine data about the prevalence and incidence of BM in both advanced and metastatic NSCLC with targetable genomic alterations. Of the 24,784 included patients, almost 30% with advanced NSCLC were found to have BM at the time of diagnosis. Among those without BM at diagnosis, approximately 11% will develop BM per year. At a median of two years from diagnosis, 55% of patients with advanced and metastatic NSCLC will have BM, either because they had them at presentation or they developed them in the intervening period. *ALK*-positive (17.0%/year) and *EGFR*-positive (15.8%/year) NSCLC have higher rates of BM development than wild type (12.5%/year).

BM are frequently encountered in NSCLC, with primary lung cancers being responsible for 50% of all diagnosed BM.[35,36] Prior to this study, population estimates of prevalence at diagnosis varied between 20 and 60%.[37,38] This study provides clarification of this figure to approximately 30%. The high prevalence at diagnosis indicates that cranial imaging during baseline staging, particularly in metastatic lung cancer, should be considered. Existing guidelines do not advocate this practice, often citing low prevalence for this recommendation.[39-42] There have been few studies investigating the cost-benefit of these programmes, but it is clear that BM in NSCLC carry a significant symptomatic and economic burden.[29,43,44] Detection while asymptomatic could improve quality of life, expedite treatment decisions and increase the pool of patients eligible for surgical and non-surgical treatments.[29,45-47] At 2 years after diagnosis, 55% of patients will have BM. Therefore, the burden of BM in the natural disease course of advanced and metastatic NSCLC is high. Resources and scientific funding should reflect this high prevalence, incidence, and burden- with studies focussed on preventing, managing, and treatment of BM.

The high rates of development of BM in patients who did not have them at presentation – 11% overall, 12.5% for wild type NSCLC - indicate that BM remain a significant component of the advanced and metastatic NSCLC disease course.[48] There was no difference in cumulative incidence in Stage III and Stage IV groups- suggesting that brain imaging should be considered in patients already with stage III disease and beyond. Our analysis illustrates that patients with *ALK*-positive and *EGFR*-positive NSCLC had higher rates of BM development

than other genomic alterations and wild type tumours, which is supported by the literature.[49,50] The association of BM with particular subgroups may drive novel preclinical research around mechanisms of BM development even if initial studies suggest NSCLC lung driver mutations may lack concordance in subsequent BM.[51] Other genomic alterations have been postulated to be associated with metastasis development- such as *ROS1, MET, and RET.*[52-55] However, our study does not support a higher rate of BM in these cases compared to wild-type cohorts[52,56,57] perhaps due to these series having a high usage of TKIs and targeted treatments.

There is ongoing debate regarding the use of whole brain radiotherapy (WBRT) to reduce BM incidence, and the balance between significantly reducing new BM incidence,[24] and risk of cognitive decline.[11,12] We explicitly excluded studies using PCI in this analysis. Stereotactic radiosurgery (SRS) for confirmed BM may extend survival whilst mitigating cognitive effects with the aim of reduced morbidity from BM.[58] Nonetheless, this study was not designed to examine the effects of different forms of radiotherapy on BM incidence or development and this question has been addressed in other studies.[59]

Significant differences were noted between groups with different driver mutations- most notably *EGFR* and *KRAS* having increased rates of BM development (0.16 and 0.17 respectively) and *MET* (0.08) having the lowest. It has been established in previous studies that many patients with BM have *EGFR*, *ALK*, and *KRAS* mutations, but the explanations behind this association are yet to be fully elucidated.[60] Lower rates could be the result of a lack of studies in the lesser encountered mutations,[28,61] or the presence of more effective treatments that may penetrate the blood-brain barrier.[28] We also observed significant differences within included studies of the same genomic alteration. In the *EGFR* group, one study had a incidence rate of 0.04 per-year,[60] and three studies had rates of 0.4 per-year.[62-64] Likewise, for *KRAS*, one study had an incidence rate more than double the pooled rates.[31] This study included patients treated with crizotinib, a first generation TKI, which is known to be less efficacious at preventing BM compared to second and third generation TKIs.[6,30] Variations in treatment paradigms, monitoring and surveillance, and study quality may all affect the differential rates observed in our review.

In summary, our results have important implications for clinical practice and future research. BMs are a significant cause of morbidity and mortality in NSCLC, and close

monitoring of higher risk groups or imaging for the presence of BM at diagnosis could allow earlier detection of asymptomatic BM which may be more amenable to therapies such as radiosurgery, surgery or targeted agents. Identifying the factors that drive the process of BM and identifying genomic targets could help prevent CNS spread and subsequent progression.[51,65,66] Trials of both *EGFR* and *ALK* inhibitors have shown reduced risk of BM and improved overall survival.[67,68]

Limitations

This study has several limitations. Firstly, many studies were retrospective, and some were excluded due to not having a median follow-up time, or stage-specific data. Additionally, this study did not include incidence for Stage I and Stage II lung cancer. While these populations have longer survival, the incidence of BM is much lower, and therefore the clinical benefits of detection are reduced.[69,70] We also did not include articles in languages other than English – this excluded at least one study from inclusion.[71] In order to obtain pooled estimates of prevalence and incidence, studies including patients on mixed kinase inhibitors and in some cases immunotherapy were pooled. This is certainly a confounder as the effects of these therapies on BM in treatment naïve patients is poorly understood and indeed CNS penetrance of many novel agents is unknown. This may explain the lower rates of incidence in *ALK* and *ROS* groups reported here compared to existing literature.[72] We mitigated this by analysing separately the data for patients treated with known CNS penetrant TKIs, but detail about agents and incidence rates was not given in all studies and individual patient data to allow survival analyses was not available. There was also significant intra-genomic variation in BM incidence for studies that examined the same mutation- this may also be influenced by experimental treatment paradigms offered by the studies, differences in case mix, and other factors. We also used median follow up time rather than mean follow up time to calculate cumulative incidence. Since survival times are often skewed, this may have underestimated the person time at risk and overestimated incidence. However, we are unable to assess the extent to which this is the case without individual patient data.

The studies included in the meta-analysis also demonstrated significant heterogeneity and publication bias. However, we aimed to include all studies in our analysis to best ascertain the natural history and rates of BM and mitigated the between-study heterogeneity by running random effect models. Finally, while we included over 15 *EGFR*-positive studies, the rarer the alteration, the fewer the studies were available for the meta-analysis. This is to be expected given the nature of these alterations, but is nonetheless a significant limitation which can hopefully be addressed in future with accrued data.

CONCLUSION

This is the first systematic review and meta-analysis to evaluate the prevalence and incidence of BM in advanced and metastatic NSCLC, stratified by molecular and genomic alterations. The high prevalence at diagnosis (around 30%) and incidence during follow up (11% per year) indicates careful attention to the current brain screening and follow up arrangements both locally and nationally are needed and consideration to personalising such pathways in higher risk patients (*ALK* and *EGFR*-positive) is needed.

CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest.

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DATA SHARING STATEMENT

All files and manuscript data are available, by contacting the corresponding author.

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FIGURE LEGENDS

Figure 1. PRISMA Flow diagram, of study selection for inclusion in this review and meta-analysis.

Figure 2. Forest plot of incidence per year in *EGFR*-positive advanced NSCLC.

Figure 3. Panel of forest plots of incidence rates per year in ALK (all patients), ALK (with patients receiving TKI removed), KRAS, ROS-1, RET, and MET-positive advanced NSCLC.

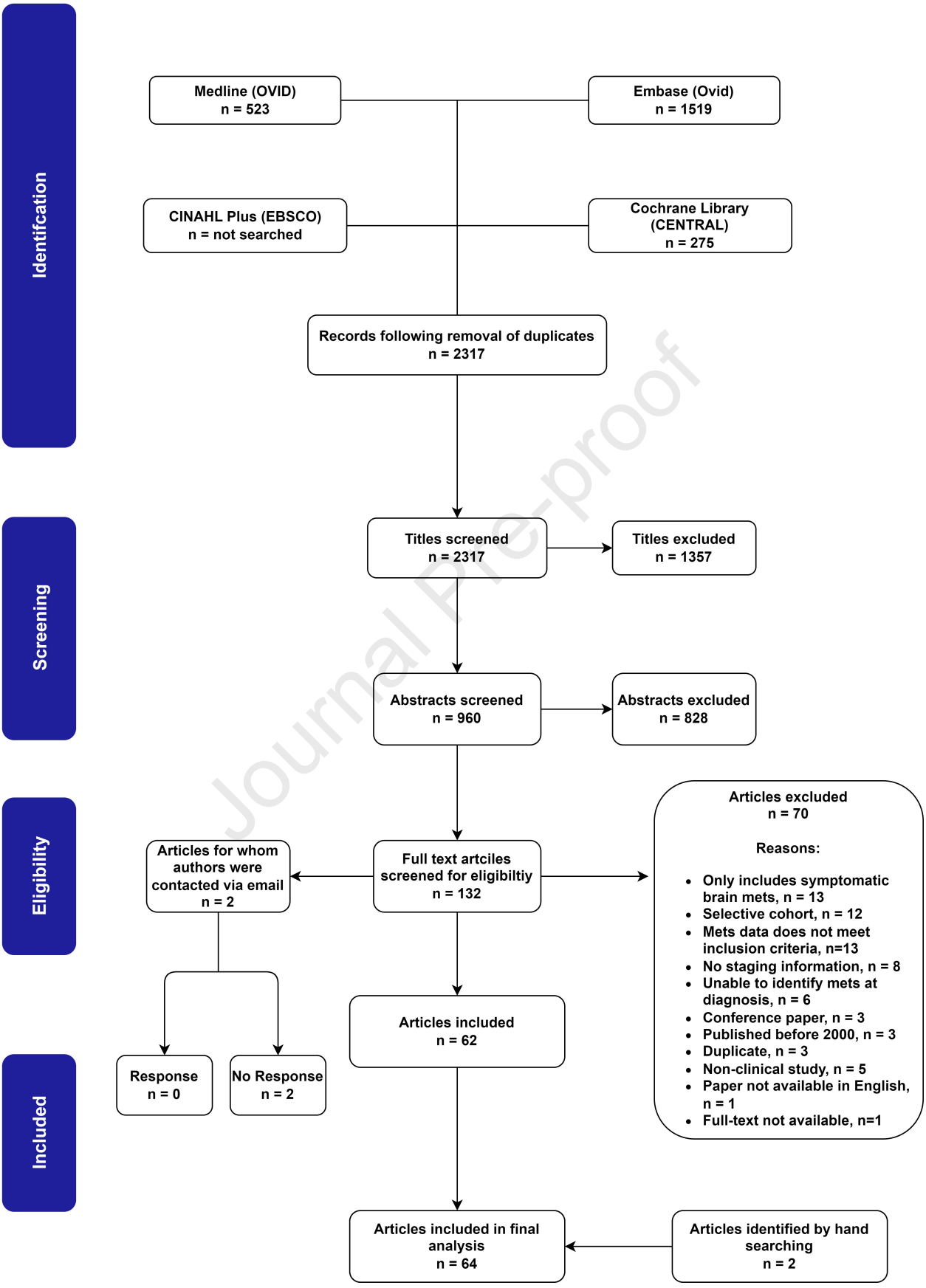
Figure 4. Violin plot (fixed width 1) and histogram of combined raw incidence rates per year, stratified by genomic alteration (diamond= mean, red line= comparative line across Wildtype mean [0.14], dots=each study). *Note BRAF, HER-2 not included due to having one study with data available.

TABLES

Table 1: Incidence and prevalence of brain metastases in advanced NSCLC, stratified by genomic alterations. *=TKI removed.

	Included studies (Number of patients)	Number with BM (%)		Pooled Prevalence (%; 95% CI)
Prevalence				
All studies	45 (24,784)	6544 (26.4)		28.6 (26.1-31.1)
Stage IV	31 (19,381)	4958 (25.6)		26.8 (24.0-29.6)
Stage III	2 (396)	NA		NA
Mixed	12 (5007)	1480 (29.6)		33.1 (27.3-39.2)
EGFR	22 (3990)	1082 (30.6)		29.4 (24.5-34.5)
ALK	9 (782)	248 (31.7)		34.9 (23.4-47.3)
KRAS	8 (695)	208 (30.0)		30.2 (24.4-36.2)
ROS1	3 (141)	43 (34.3)		30.1 (21.4-39.5)
RET	3 (203)	57 (28.0)		32.2 (18.6-47.3)
Wild-type	9 (14447)	3689 (25.6)		28.8 (23.7-34.2)
Incidence per year				
	Included studies (Number of patients)	**Median follow-up in months (IQR)**	**Number developing BM (%)**	**Pooled Incidence (%; 95% CI)**
All studies	40 (9058)	24.0 (16.3-36.0)	1745 (19.3)	0.11 (0.09-0.13)
Stage IV	14 (2760)	18.6 (14.8-29.0)	398 (14.4)	0.12 (0.09-0.15)
Stage III	11 (1949)	24.0 (21.0-38.3)	449 (23.0)	0.11 (0.08-0.15)
Mixed	15 (4349)	24.1 (16.4-36.0)	898 (20.6)	0.10 (0.08-0.13)
EGFR	15 (2556)	20.3 (12.5-25.2)	638 (25.0)	0.16 (0.11-0.21)
*ALK**	7 (794)	36 (24.0-36.0)	284 (31.2)	0.17 (0.11-0.26)
KRAS	4 (286)	21.4 (15.8-26.8)	44 (15.4)	0.10 (0.06-0.17)
ROS1	3 (117)	30.0 (22.1-NA)	36 (30.8)	0.13 (0.06-0.28)

RET	2 (113)	39.5 (19.5-NA)	44 (38.9)	0.12 (0.08-0.18)
C-MET	2 (72)	40.0 (39.0-NA)	17 (23.6)	0.08 (0.07-0.11)
Wild-type	14 (2156)	22.5 (14.8-32.6)	474 (22.0)	0.13 (0.11-0.16)
Combined prevalence and incidence				**Pooled proportion (%; 95% CI)**
All studies	21 (6425)			55.0 (32.8-91.0)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Embase (Ovid)
n = 1519
CINAHL Plus (EBSCO)
n = not searched
Cochrane Library
(CENTRAL)
n = 275
Records following removal of duplicates
n = 2317
Titles screened
n = 2317
Titles excluded
n = 1357
Abstracts screened
n = 960
Abstracts excluded
n = 828
Articles for whom authors were contacted via email
n = 2
Full text artciles screened for eligibiltiy
n = 132
Articles excluded
n = 70
Reasons:
Only includes symptomatic brain mets, n = 13
Selective cohort, n = 12
Mets data does not meet inclusion criteria, n=13
No staging information, n = 8
Unable to identify mets at diagnosis, n = 6
Conference paper, n = 3
Published before 2000, n = 3
Duplicate, n = 3
Non-clinical study, n = 5
Paper not available in English, n = 1
Full-text not available, n=1
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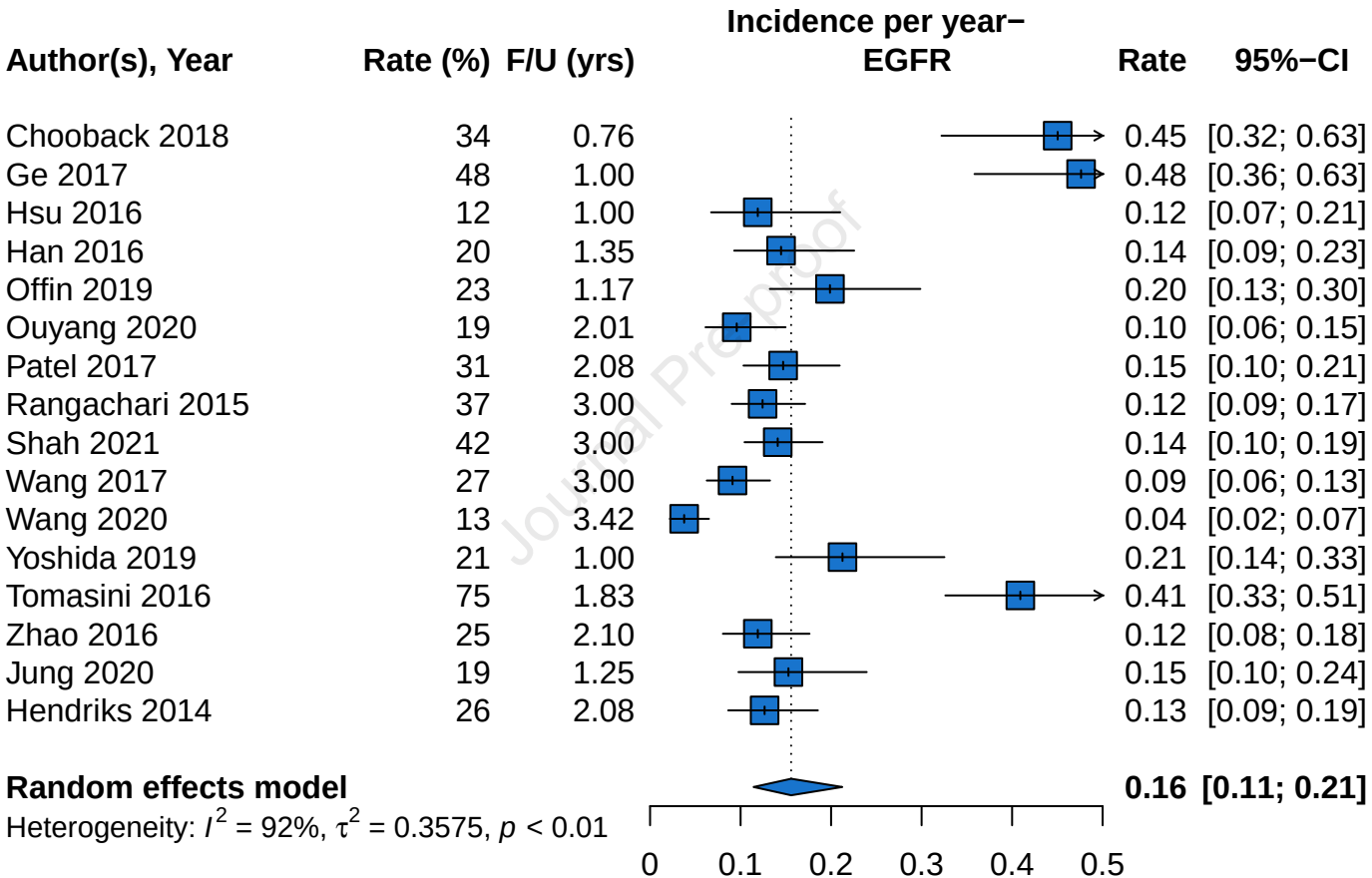

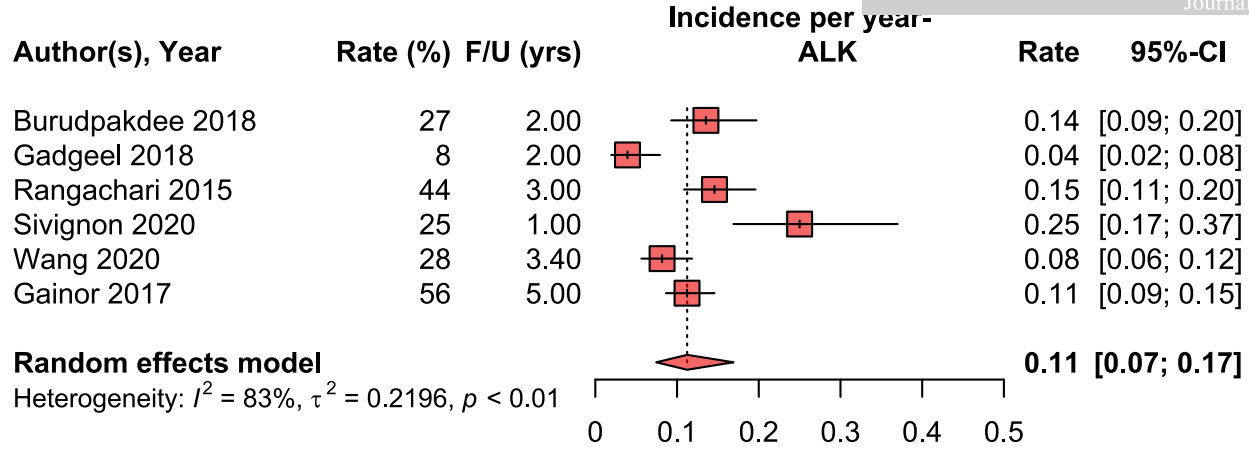

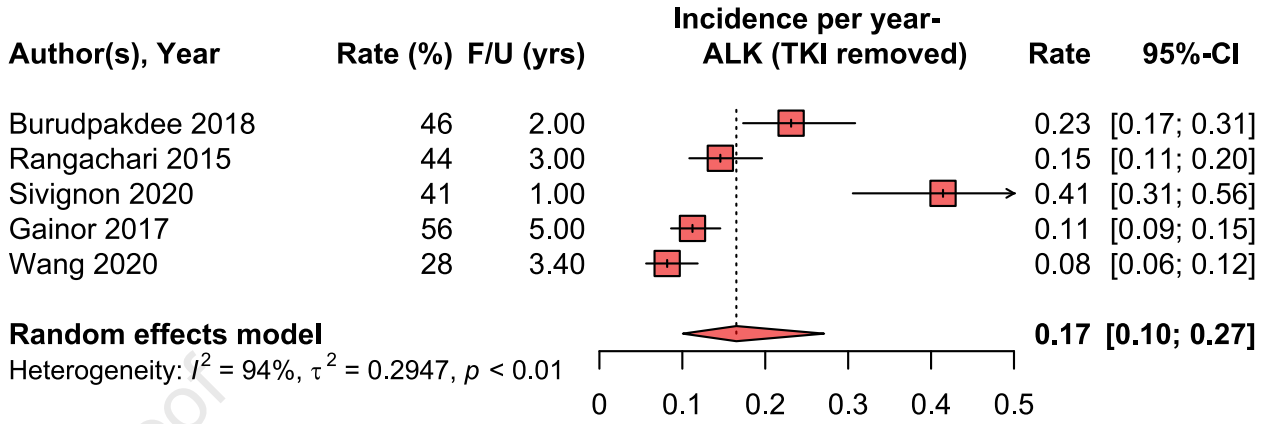

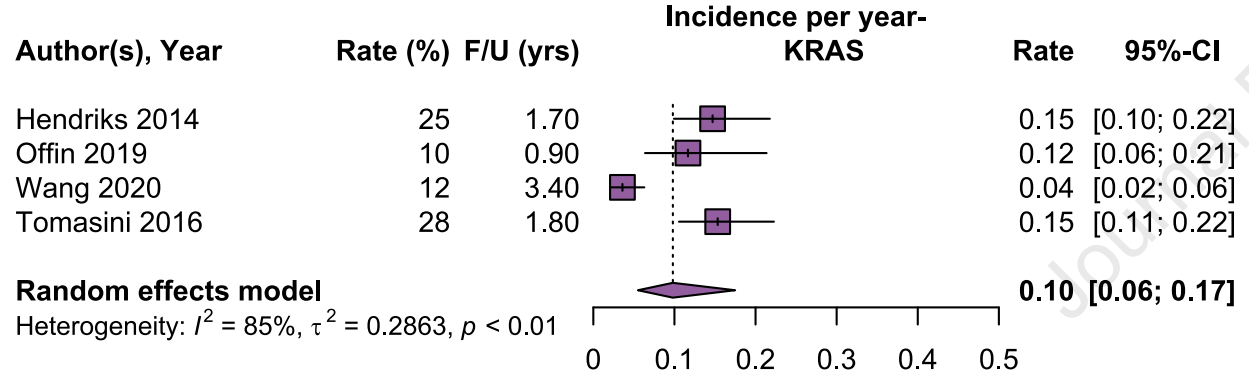

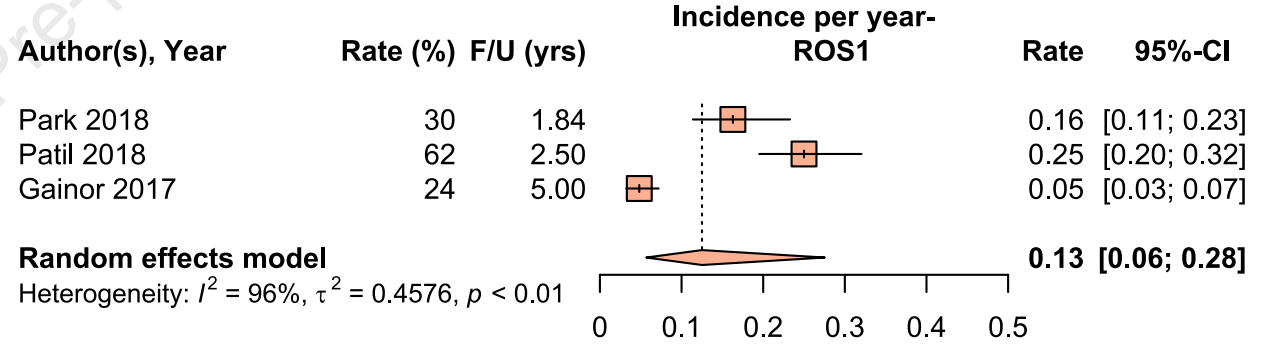

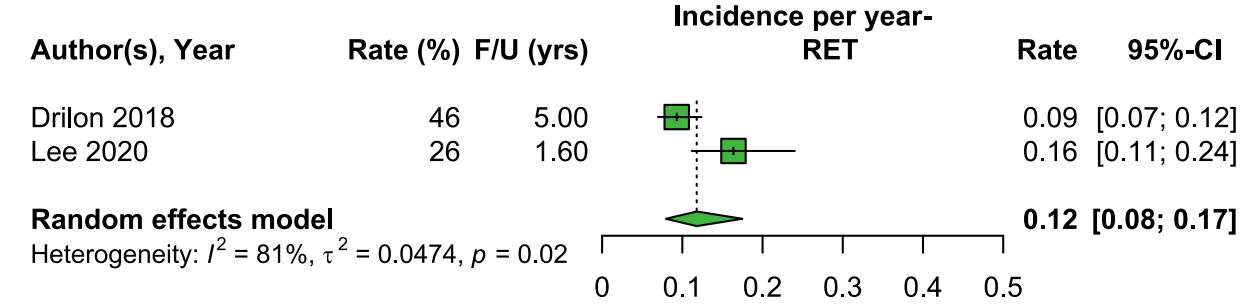

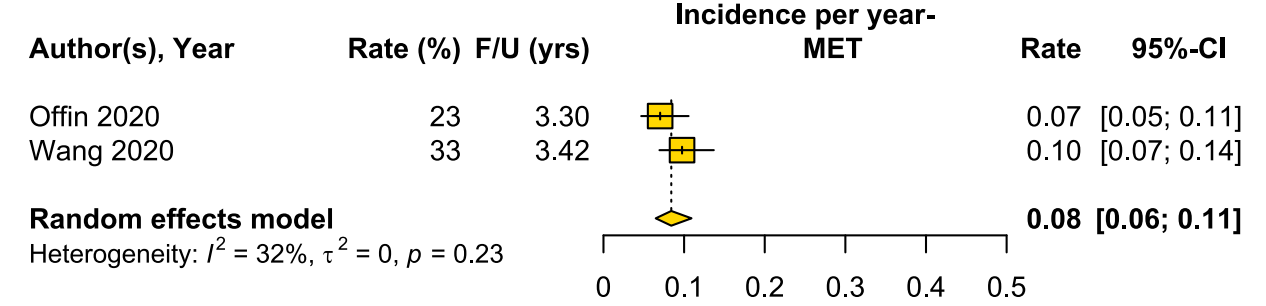

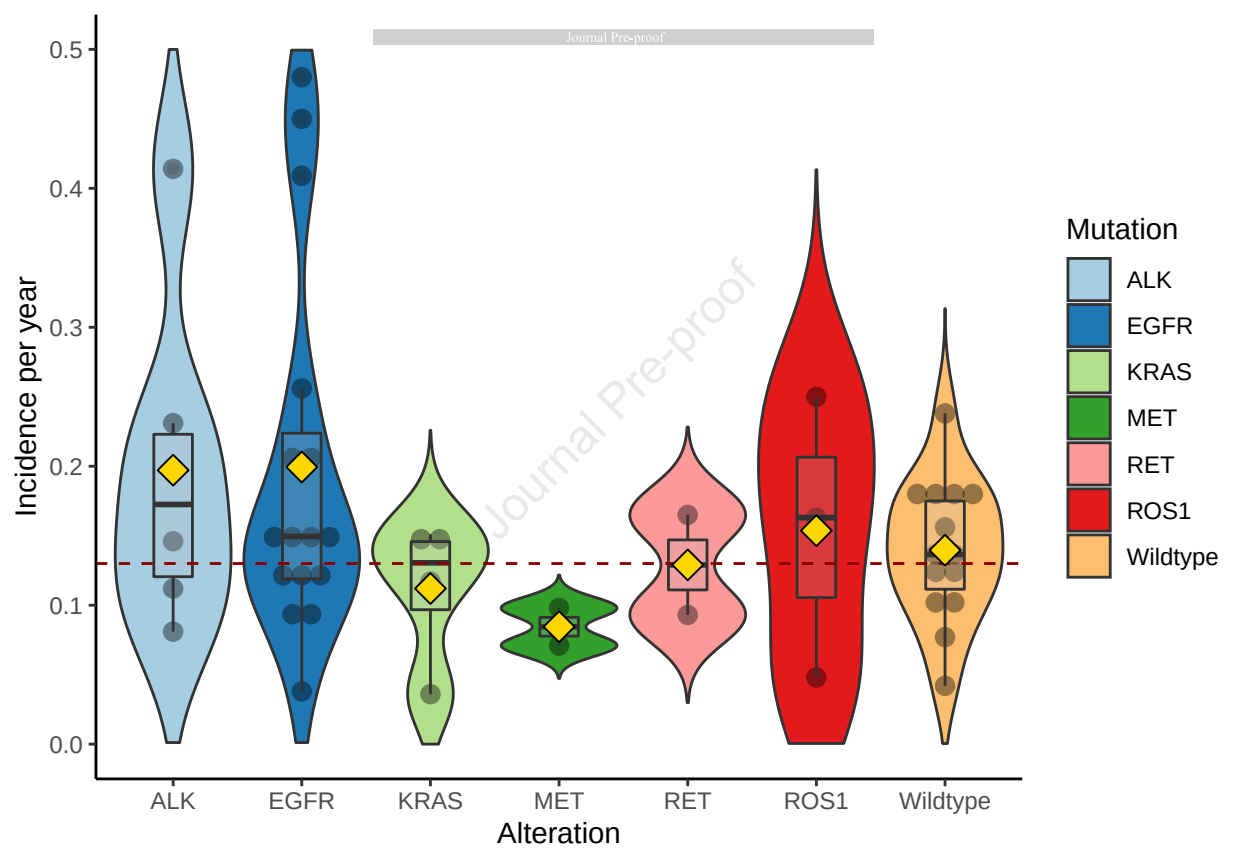

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