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Association between unilateral tonsillar enlargement and lymphoma in children: A systematic review and meta-analysis

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Contents

Abstract

Lymphoma is the most common head and neck malignancy in children, and palatine tonsils asymmetry is the most frequent clinical manifestation of tonsillar lymphoma. However, several studies with children with tonsillar asymmetry found no case of lymphoma, showing that the relationship of tonsillar asymmetry with lymphoma is unclear. In this review, we aimed to identify the association between tonsillar asymmetry and tonsillar lymphoma in children by conducting systematic reviews of the literature on children with palatine tonsil lymphoma and tonsillar asymmetry. Articles comprising the paediatric age group (up to 18 years) with information concerning clinical manifestations of tonsillar lymphoma or the diagnosis of the tonsillar asymmetry were included. The main cause of asymmetry of palatine tonsils was lymphoid hyperplasia, followed by lymphoma and nonspecific benign changes. The asymmetry of tonsils was present in 73.2% of cases of lymphoma. There was an association between asymmetric palatine tonsils and lymphoma, with a likelihood ratio of 43.5 for children with asymmetry of palatine tonsils and 8938.4 for children with asymmetry of tonsils and other signs of suspicion for malignancy. We also provide recommendations on the management of suspicious cases of palatine tonsil lymphoma.

Keywords: Lymphoma; Children; Tonsil; Tonsil asymmetry; Unilateral tonsillar enlargement

Abbreviations: PT, palatine tonsils; LR, likelihood ratio; CI, confidence interval.

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1. Introduction

Lymphoma is the third most common malignancy of childhood, accounting for approximately 12% of all cancers in individuals under 15 years of age [1].

In the paediatric population, lymphomas are the most frequent malignant tumours of the head and neck, and non-Hodgkin lymphoma is the most common type [2]. The extranodal involvement is more common in non-Hodgkin lymphoma when compared with Hodgkin lymphoma, and the palatine tonsils (PT) are the most frequent site of extranodal involvement in non-Hodgkin lymphomas [3].

Knowledge of the most frequent clinical manifestations of PT lymphoma is critical for detection and early diagnosis [4], allowing treatment during the initial stages and increased disease-free survival and overall survival [5–7]. The size of tonsillar lymphoma also has a direct relationship with prognosis [8].

In a study with 47 children with tonsillar asymmetry and 43 children with symmetric tonsils undergoing tonsillectomy, no difference in the PT volumes between groups was observed, with the apparent asymmetry resulting from the difference in the depth of the tonsillar fossa [9]. In another study of 13 children with asymmetric PT, there were no cases of lymphoma in these children and no difference in the PT sizes when compared to children without asymmetry [10].

Other studies with patients with apparent asymmetry of PT found no difference between the PT sizes in 39–52% of cases, and in most of the patients, the PT considered bigger was smaller than the contralateral [11–13]. Clinical asymmetry in these cases was attributed to variations in depth of the tonsillar fossa or to anterior tonsillar pillar asymmetry.

The asymmetry of PT is the most common clinical manifestation in children with PT lymphoma and is present in 72.7% of patients, followed by alteration of the appearance of PT and cervical lymphadenopathy [4]. The correlation of the apparent asymmetry of PT with the asymmetry of PT sizes after tonsillectomy is unclear, and the asymmetry is a common finding in healthy children, present in 1.7% of children aged 4–17 years [14], and therefore, the relationship between tonsillar asymmetry and PT lymphoma is not clear.

The relationship of tonsillar asymmetry with PT lymphoma in children remains controversial and there are no reviews with a high level of evidence on the subject in the literature. To establish this relationship, this article intends to calculate the likelihood ratio (LR) of the presence of PT asymmetry with the presence of PT lymphoma.

In diagnostics, the likelihood ratio of a test provides a way to estimate the pre- and post-test probabilities of having a disease. The LR is the ratio of the sensitivity divided by 1 minus the specificity of a test. It determines how many times the likelihood of a given test result increases in the presence of a positive test compared with the likelihood of a negative test. In this case, it will determine how many times the presence of asymmetric PT increases the chance of the presence of PT lymphoma in children; currently, this relationship has not been established.

This study aimed to perform a systematic review of the literature on the presence of PT asymmetry at the time of diagnosis of PT lymphoma in paediatric patients and a systematic review on the presence of PT asymmetry in children regardless of its cause. Furthermore, we evaluated the relationship of PT asymmetry with PT lymphoma and determined the likelihood ratio of this indication of lymphoma.

2. Methods

The systematic reviews and meta-analysis followed the criteria defined by the PRISMA statement [15] and the current recommendations of the Cochrane Collaboration.

2.1. Study selection and search strategy

The following databases were systematically used by two authors (ACG, GMC): PubMed/MEDLINE, LILACS, Cochrane, Scopus and SCIELO. Two searches were performed on these databases. To detect cases of PT lymphoma in children, the first systematic review searched the following MeSH terms and free text words “tonsillar lymphoma and children”. To identify cases of tonsillar asymmetry, the second search was made by the following MeSH terms and free text words “unilateral tonsillar enlargement or tonsillar asymmetry and children”. The search was restricted to articles in English, Spanish and Portuguese languages related to PT lymphoma in children up to 18 years old, from January 1996 to December 2013.

Two authors were responsible for selecting all articles; all abstracts were read and from the information contained therein, if there was the possibility of cases of PT lymphoma or tonsil asymmetry in children, the articles were completely read. From the articles read, those that covered the considered paediatric age range and contained information of the clinical manifestations of PT lymphoma at diagnosis or cases of tonsillar asymmetry were included. The inclusion of articles was reviewed by both authors. Review articles without clinical cases and those that did not allow the definition of the presence or absence of PT lymphoma for each patient were excluded. Only cases of PT lymphoma confirmed by histopathology were considered.

The following data were assessed from the articles: number of cases of PT lymphoma, gender, age, tonsillar asymmetry, classification used to determine the tonsillar asymmetry, aetiology in other cases of tonsillar asymmetry, authors and year of publication. Reported information in articles was considered and clinical information of the patients not reported was considered absent.

The children in the study were classified according to the presence or absence of PT asymmetry, presence of PT lymphoma and also according to the presence of other suspicion factors for PT lymphoma. The considered suspicion factors

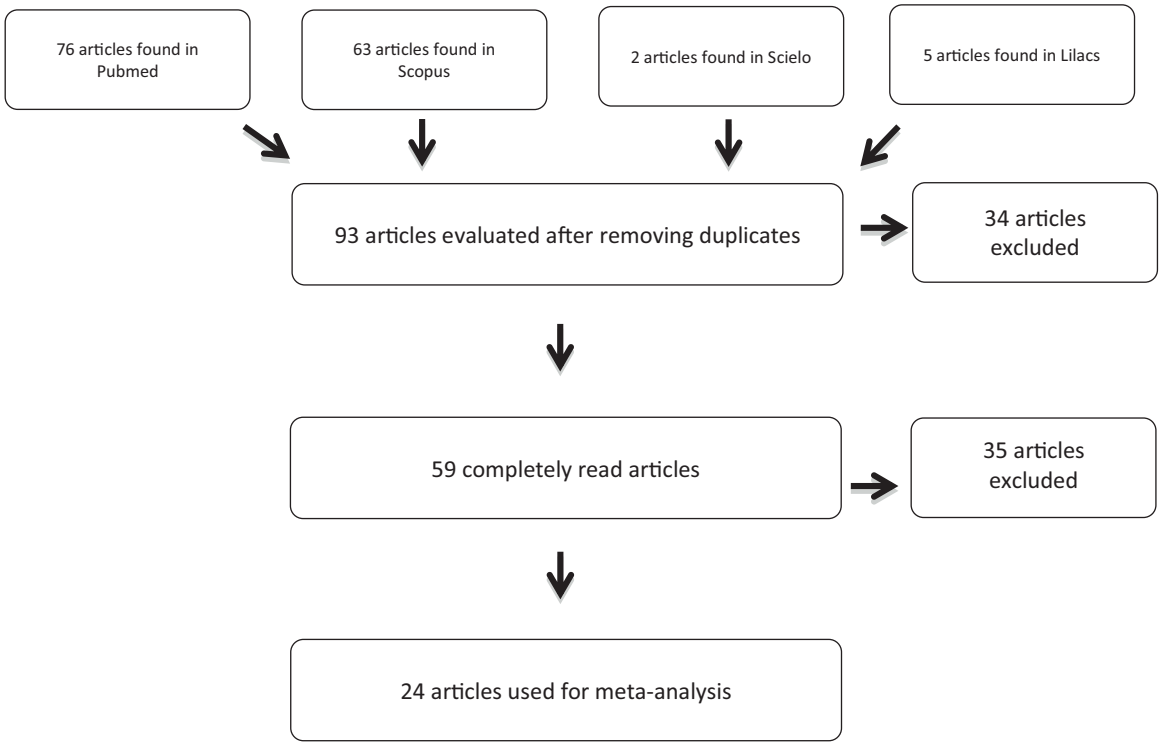

Fig. 1. Flowchart of articles included and excluded in the search of PT lymphoma.

for PT lymphoma were an alteration in the appearance of PT (colour alteration or visible lesion in PT), cervical lymphadenopathy larger than 3 cm, dysphagia, snoring, recurrent fever, weight loss greater than 10%, immunosuppression or prior radiotherapy.

The sensitivity of the PT asymmetry as a test for the diagnosis of PT lymphoma was calculated as the percentage of children with PT asymmetry among all those diagnosed with PT lymphoma. Since the prevalence of children without PT asymmetry and without lymphoma was lower than expected for the general population due to our search strategy, we also used the specificity of 1.7%, which is the prevalence of children with PT asymmetry without PT lymphoma [14].

We performed a meta-analysis of the data and calculated the likelihood ratio for the presence of PT asymmetry in the presence of PT lymphoma in children for the group of children with and the group without the presence of other factors of suspicion for lymphoma, with a confidence interval of 95%. The LR was calculated by dividing the sensitivity by (1 minus the specificity) for each study group.

The study was approved by the research ethics committee of the institution.

3. Results

One hundred and forty-six articles were found in the search for articles with PT lymphoma in children; 53 were excluded for being duplicates. Of the 93 included studies, 30 were excluded because they did not contain clinical data, since these studies focused on pathology, immunology and gene expression. In addition, two others were excluded because they were literature reviews without cases, and two other articles were excluded because they were related to cerebellar tonsils. In total, 59 studies were read completely; 13 were excluded for not having detailed information of the cases; 11 were excluded because they did not allow differentiation of children from adult cases; seven articles were excluded for being cases of children without PT lymphoma or PT asymmetry; two articles were excluded as they were revisions without cases; one article was excluded for being an editorial; and one article was excluded for possessing the same sample of another included article. Finally, 24 articles remained for the meta-analysis (Fig. 1).

Sixty-two articles were found in the search for articles with tonsillar asymmetry or unilateral tonsillar enlargement in children; however, 30 articles were excluded for being duplicates, leaving 32. Five of the 32 included studies were excluded because they were related to cerebellar tonsils. Twenty-seven studies were completely read; seven were excluded because it was not possible to differentiate adult from children cases; four were excluded because they did not have histopathological results; two were excluded because they did not contain cases of tonsillar asymmetry; one was excluded due to cases being only in adults; and one was excluded because it had the same sample of another included

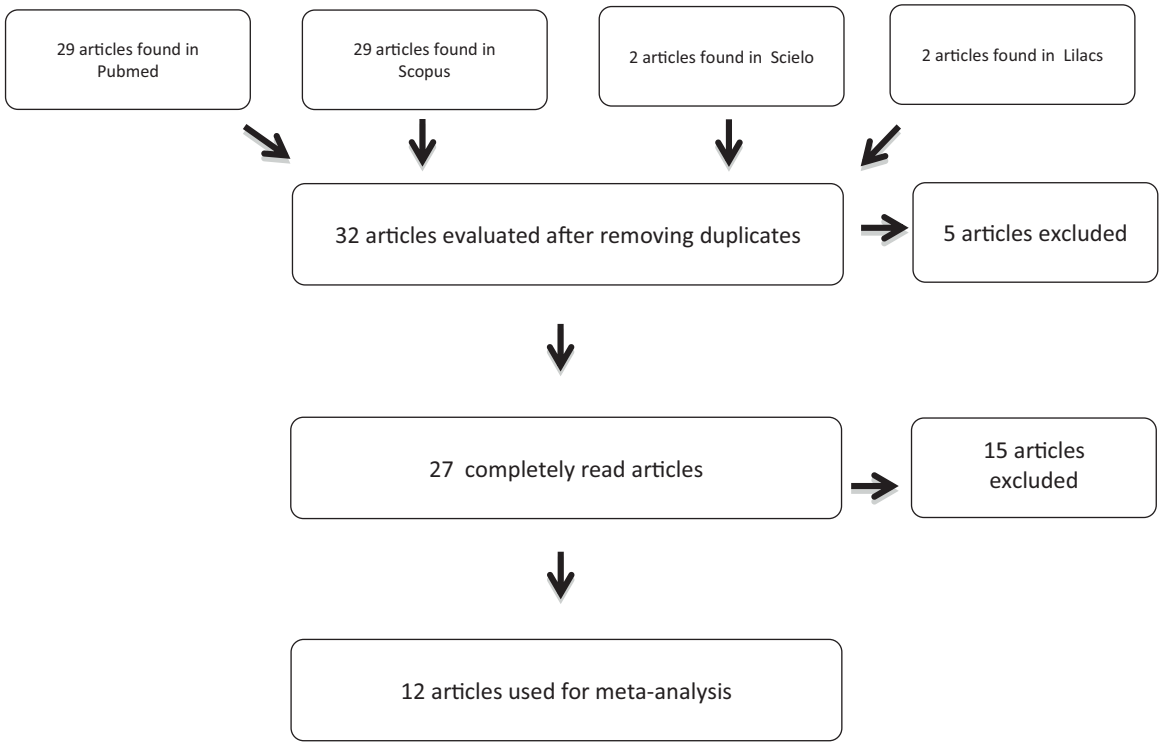

Fig. 2. Flowchart of articles included and excluded in the search of unilateral tonsillar enlargement in children.

article. Finally, 12 articles remained for the meta-analysis (Fig. 2).

Twenty-nine articles were selected after excluding duplicates in the search for PT asymmetry and PT lymphoma (Table 1) [9,10,12,13,16–40].

The age of children with PT lymphoma was described in 69 of 71 cases, ranging from 1 to 17 years, with a mean of 7.7 years.

Among the 71 children with PT lymphoma, 52 had PT asymmetry, 46 of them with other suspicious factors of malignancy, and in six children, PT asymmetry was the only clinical manifestation of lymphoma. Concerning the 19 children with lymphoma and without PT asymmetry, 16 had other suspicious clinical manifestations of neoplasia, and three had no suspicion for malignancy with an unexpected diagnosis after histopathological examination. A table with all the children included in the study shows the distribution of children with PT asymmetry alone or associated with other clinical manifestations of malignancy (Tables 2 and 3).

From the 27 articles of children containing asymmetric PT, no classification was used to define the PT asymmetry in 22 articles, and the asymmetry was just described as being that one of the PT was greater than the other or that PT asymmetry was present. In four articles, the classification of Brodsky [41] was used to assess the size of each PT and to determine the presence of asymmetry, while in one article the classification of Friedman [42] was used to evaluate the size of PT and the presence of PT asymmetry.

From the 284 children with PT asymmetry, the cause of the asymmetry was due to lymphoid hyperplasia in 94 children, lymphoma in 52, chronic tonsillitis in 51, intratonsillar abscess in nine, actinomycosis in five, acute tonsillitis in five, atypical lymphoid proliferation in one, Proteus syndrome in one, and due to unspecified benign findings in 66 children.

PT asymmetry was present in 52 of 71 patients with PT lymphoma, which results in a sensitivity of 73% to this clinical sign. The asymmetry was absent in 225 of 457 patients without PT lymphoma, resulting in a specificity of 50.7%, and thus the likelihood ratio for PT asymmetry was 1.44 (CI: 1.22–1.70).

As the prevalence of PT asymmetry in children without PT lymphoma was very high in our study (50.7%) due to the search strategy of the articles that focused on patients with PT lymphoma or PT asymmetry, when considering the prevalence of children with asymmetric PT of 1.7% (Table 4), the LR for PT asymmetry is 43.55 (CI: 29.73–63.79).

To evaluate the association of other suspicious signs of malignancy in children with PT lymphoma for children with PT asymmetry, we arranged the children with PT asymmetry according to the presence of other signs of malignancy (Table 5) and found a LR of 205.2 (CI: 28.96–1454). Therefore, when considering children with PT asymmetry and other signs of malignancy, the LR for PT lymphoma is 8938.43 (CI: 860.98–92 750.66).

Table 1
Articles included in the systematic review and the number of patients with lymphoma and PT asymmetry in each study [9,10,12,13,16–40].

Authors	Patients with lymphoma	Patients with asymmetry
Amit et al. [16]	1	1
Ballin et al. [17]	0	39
Banthia et al. [18]	1	1
Berkowitz et al. [12]	7	53
Booth et al. [19]	3	1
Broughton et al. [20]	1	0
Cianci et al. [21]	1	1
Dolev et al. [22]	6	6
Garavelo et al. [23]	2	1
García-Ortega et al. [24]	1	1
Gheorghe et al. [25]	1	0
Guimarães et al. [26]	2	2
Kraus et al. [27]	0	1
Harley et al. [9]	0	47
Meirelles et al. [28]	2	2
Oluwasanmi et al. [29]	0	19
Papouliakos et al. [30]	1	1
Pelier et al. [31]	1	1
Prim Espada et al. [32]	1	9
Sahni et al. [33]	0	1
Sayed et al. [34]	29	19
Smitheringale [35]	5	3
Spinou et al. [13]	0	47
Tewfik et al. [36]	3	3
Ulualp et al. [37]	0	9
van Lierop et al. [10]	1	13
Williams et al. [38]	1	1
Yadav et al. [39]	0	1
Zeglaoui et al. [40]	1	1
Total	71	284

Table 2
Distribution of the children according to the presence of PT asymmetry and PT lymphoma.

	With PT lymphoma	Without PT lymphoma	Total
With PT asymmetry	52	232	284
Without PT asymmetry	19	225	244
Total	71	457	529

4. Discussion

Considering the prevalence of PT asymmetry in the children of 1.7%, the likelihood ratio found for PT asymmetry was 43.55, which represents a significant increase in the suspicion of PT lymphoma, but when the asymmetry is associated with other signs of malignancy, the LR is 8938.43, *i.e.*, much higher and thus increasing the suspicion for PT lymphoma.

The use of LR to evaluate the performance of diagnostic tests is recommended and is considered a convenient way to express the results of systematic reviews and meta-analyses of diagnostic studies [43].

This was the first systematic review and meta-analysis that evaluated the relationship between the presence of PT asymmetry and PT lymphoma in children. Because PT lymphoma is a relatively rare condition, there are no controlled or cohort studies that examine the role of clinical manifestations for the diagnosis of lymphoma in children. We chose to include in this review case series and case reports of isolated cases, in order to increase the total number of cases and to include possible cases of PT lymphoma without tonsillar asymmetry or lymphoma cases without any clinical manifestation.

This study suffers from the inherent limitations of the model studied, and does not allow any temporal association and has the possibility of a selection bias. The methodology designed to find articles with cases of PT lymphoma or PT asymmetry in children was adequate, though the number of children without PT asymmetry and without lymphoma found in these studies was relatively low, with a prevalence of asymmetric PT of 50% in the children without lymphoma,

Table 4
Distribution of patients according to the presence of asymmetric PT and PT lymphoma, considering data from a previous study for the patients with PT asymmetry patients without PT lymphoma [14].

	With PT lymphoma	Without PT lymphoma	Total
With PT asymmetry	52	30	82
Without PT asymmetry	19	1754	1773
Total	71	1784	1855

Table 5
Distribution of patients with PT asymmetry according to the presence of other suspicious signs of malignancy.

	With PT lymphoma	Without PT lymphoma	Total
With other signs of malignancy	46	1	47
Without other signs of malignancy	6	231	237
Total	52	232	284

Table 3
Distribution of the children according to the presence of PT asymmetry, PT lymphoma and the presence of other suspicious clinical manifestations of lymphoma.

	With other suspicious clinical manifestations		Without other suspicious clinical manifestations	
	With PT lymphoma	Without PT lymphoma	With PT lymphoma	Without PT lymphoma
With PT asymmetry	46	1	6	231
Without PT asymmetry	16	12	3	213
Total	62	13	9	444

which is not expected for the general population. For this reason, aiming to circumvent this bias, we chose to perform the calculation of the LR using the prevalence of asymmetric PT in healthy children (without PT lymphoma) of 1.7%, which was described in the previous study [14].

Interestingly, few studies have used any classification to define the presence of tonsillar asymmetry: only five articles used a classification, representing 18.5% of the articles with cases of asymmetry of PT. The Brodsky classification was most often used.

Most cases of PT asymmetry in children were due to benign causes, and the most frequent histopathological finding was lymphoid hyperplasia. In 211 (74.2%) cases, the cause of asymmetry was nonspecific benign disorders, such as chronic tonsillitis or lymphoid hyperplasia. Other less-common causes of benign findings were intratonsillar abscess, actinomycosis and a case of Proteus syndrome. The lymphoma was the cause of PT asymmetry in 18.3% of 284 children with asymmetry of PT. We believe that this prevalence of lymphoma in this population is high and can be influenced by the inherent selection bias in the study design, since the cases of children with serious illnesses as a cause of PT asymmetry tend to be more reported in the literature than cases of children with asymmetry of PT caused by benign disorders such as chronic tonsillitis.

Several studies that evaluated the presence of PT lymphoma in children with PT asymmetry found no cases of lymphoma in this group [9,12,13,17,29,32]. Probably, no cases of lymphoma were present in these studies because lymphoma is a rare cause of isolated PT asymmetry, and none of these studies had a sample large enough to have a case of PT lymphoma. However, when we look at the children with PT lymphoma in this study, out of 71 cases of PT lymphoma, PT asymmetry was present in 52 cases (73.2%), as observed in a previous study that showed that tonsillar asymmetry is the main clinical manifestation of children with PT lymphoma [4]. In 46 (88%) of these 52 cases, the asymmetry was associated with other signs of malignancy, and in six (8.4%) of the 71 cases of PT lymphoma, PT asymmetry was the only reported clinical manifestation.

Further, three cases of lymphoma were incidentally found after tonsillectomies, without any previous suspicion for lymphoma [19,23]. Randall et al. evaluated the need for routine histopathological examination after tonsillectomy with or without adenoidectomy in children and in adults, and concluded that the incidence of incidental malignancy is rare, and histopathological examination should only be performed in the presence of suspicion for malignancy [44].

Based on our findings, we conclude that despite the chance of PT lymphoma in children with PT asymmetry being low, there is an association between PT asymmetry and lymphoma. Seeking an early diagnosis of PT lymphoma in children, we recommend that all children with asymmetry of PT should be properly examined and other clinical manifestations of suspicion for PT lymphoma should be sought, since the presence of any of them increases the risk for lymphoma by 205 times. If the child presents with isolated asymmetric PT, a clinical follow-up is important to observe the appearance of any other sign of suspicion, and PT asymmetry should be monitored, noting whether it remains the same or if there is progression of asymmetry. In the case of onset of other signs of malignancy or progression of asymmetry, tonsillectomy is recommended for histopathological evaluation. If the child remains with asymmetric PT without any modification of the initial clinical status, we recommend only a less-frequent clinical follow-up, since this asymmetry may only be apparent or can be attributed to benign causes.

We also recommend that the PT of children with isolated PT asymmetry or unilateral tonsillar enlargement, who for various reasons are undergoing tonsillectomy, are sent for histopathological evaluation, since the chance of lymphoma in this population is higher than for the general population.

We believe that the existing and used classifications to assess PT asymmetry in studies are not accurate. The use of well-defined criteria for the characterisation of PT asymmetry and the development of a new specific classification for the asymmetry may help clarify the relationship of clinical PT asymmetry and the presence of PT lymphoma.

5. Conclusion

PT asymmetry was present in 73.2% of cases of PT lymphoma in children. There was an association between the presence of PT asymmetry in children and the presence of PT lymphoma with a LR of 43.5 for the PT asymmetry and 8938.4 for the PT asymmetry with other signs of malignancy. Compared to the normal paediatric population, the probability of the presence of PT lymphoma increases 43.5 times when PT asymmetry is present and 8938.4 times when other signs of malignancy are also present. The most frequent cause of PT asymmetry was lymphoid hyperplasia.

Conflict of interest

The authors have no conflict of interest to be disclosed.

Reviewers

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