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# Global research productivity of post-transplant lymphoproliferative disorder: a bibliometric study

Badi Rawashdeh, MD<sup>a</sup>, Saif Aldeen AlRyalat, MD<sup>b</sup>, Aasem Rawshdeh, MD<sup>c</sup>, Mohammad Abuassi, MD<sup>d,\*</sup>, Zeina Al-mansour, MD<sup>e</sup>, Ashraf El-Hinnawi, MD<sup>e</sup>

**Background:** Post-transplant lymphoproliferative diseases (PTLD) are a heterogeneous collection of neoplasms that occur after solid organ transplants (SOT). In the past 20 years, there has been a rise in PTLD research. This study aims to investigate the global research output and interest regarding PTLD using a bibliometric approach.

**Material and methods:** On 28 November 2022, the Web of Science Core Collection documents on PTLD published between 2000 and 2022 were collected and analyzed using bibliometric techniques. The VOSviewer application was utilized to visualize the annual number of publications, authors, organizations, countries, published journals, citations, and most occurring keywords. **Results:** A total of 2814 documents were retrieved, and a screening process included 1809 documents. The total number of citations was 45 239, and the average number per item was 25. Most articles (n = 747) and citations (n = 25740) were produced in the United States. Based on citations, most of the top 10 institutions that contributed were in the United States of America. The University of Pittsburgh topped the list with 2700 citations and 64 articles. The vast majority of articles were published in Pediatric Transplantation (n = 147), Transplantation (n = 124), and the American Journal of Transplantation (n = 98). Transplantation has received the most citations, 6499, followed by the American Journal of Transplantation with 5958 citations and Blood with 4107 citations.

**Conclusion:** With ongoing debates over optimal classification, Epstein-Bar virus involvement, and treatment, this topic has received significant interest from researchers in recent years. Our results can be used as a guide for future research in the field and as a framework for a more in-depth look at the scientific progress of PTLD.

Keywords: bibliometric study, post-Transplant lymphoproliferative disorder, PTLD, transplantation

## Introduction

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous collection of neoplasms that represent one of the most severe consequences following Hematopoietic Cell Transplant (HCT) and solid organ transplantation (SOT)<sup>[1,2]</sup>. PTLD have been identified for decades; the first cases were described in renal transplant recipients in 1968<sup>[3]</sup>, while the term PTLD was first introduced in 1984 by Starzl *et al.*<sup>[1]</sup>. Over the course of the

\*Corresponding author. Address: Jordan Hospital, Amman, Jordan. Tel.: + 962 790 449 828. E-mail: abuassi1997@icloud.com (M. Abuassi).

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previous twenty years, there has been mounting evidence that points to an upward trend in the number of PTLD diagnoses.

PTLD is one of the most common malignancies in recipients of solid organ transplantation (SOT) with a standardized incidence ratio (SIR) of 7.5, coming in third after Kaposi sarcoma (SIR 61.5) and nonmelanoma nonepithelial skin cancers (SIR 13.9)<sup>[4]</sup>. Moreover, given that it contributes to a significant number of cancer-related deaths in SOT recipients, PTLD has attracted a great deal of attention from researchers in recent years<sup>[4–7]</sup>. Hundreds of articles have been published on the subject of PTLD, and the number of articles has increased rapidly over the past decade, with ongoing debates about ideal classification<sup>[8]</sup>, the involvement of Epstein-Bar virus (EBV)<sup>[9,10]</sup>, and treatment<sup>[11]</sup>.

PTLD represent a complex spectrum of conditions ranging from benign lymphoid hyperplasia to malignant lymphomas, chiefly arising from iatrogenic immunosuppression post transplantation, with EBV being a pivotal aetiological agent. The pathophysiology involves the transformation of EBV-infected B cells into malignant lymphomas under the influence of immunosuppressive drugs necessary for graft survival, thereby impairing cytotoxic T-cell surveillance<sup>[12]</sup>. Diagnostically, PTLD presents as a challenge, combining clinical symptoms, radiological findings, and definitive histopathological examination including EBV detection methods<sup>[13]</sup>. Treatment is tailored and multifaceted, ranging from reducing immunosuppression to employing targeted therapies such as rituximab and innovative approaches like adoptive cell therapies, with surgical and radiological interventions for localized forms<sup>[1]</sup>. The evolving

<sup>&</sup>lt;sup>a</sup>Division of Transplant Surgery, Department of General Surgery, Medical College of Wisconsin, Milwaukee, WI, <sup>b</sup>Faculty of Medicine, Jordan University, <sup>c</sup>Division of Hematology Oncology, Department of Medicine, Jordanian Royal Medical Services, <sup>d</sup>Department of Anesthesia and Critical Care, Jordan Hospital, Amman, Jordan and <sup>e</sup>Division of Hematology Oncology, Department of Medicine, University of Florida, Gainesville, FL

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therapeutic landscape highlights the ongoing need for research to optimize management strategies in this potentially life-threatening condition.

The risk of PTLD depends on the transplanted organ, the recipient's and donor's pre-transplantation EBV serostatus, and the time interval between transplantation and diagnosis<sup>[14]</sup>. The reported incidence of PTLD varies among transplant centres<sup>[15]</sup>, likely as a result of different patient populations, allograft types, and immunosuppressive regimens<sup>[8]</sup>. Kidney transplant recipients have the lowest incidence of PTLD in the adult population (0.8–2.5%), whereas multiorgan and intestine transplant recipients have the highest incidence (20%). Recipients of liver transplants (1.0–5.5%), heart transplants (2.0–8.0%), lung transplants (3.0–10.0%), and pancreas transplants (0.5–5.0%)<sup>[8]</sup>. The time interval to PTLD development differs depending on the transplanted organ, with the longest timeframe for heart transplant recipients and the shortest timeframe for lung and heart/lung recipients in the paediatric population.

Bibliometric analysis is a widely attractive method for analyzing the fundamental characteristics of published literature, such as keyword clustering, the citation network of all manuscripts, and the collaboration network of countries, institutions, and authors of all manuscripts on a particular topic<sup>[16-18]</sup>. By studying articles on a subject from a bibliometric point of view, we can find research hotspots and patterns of change<sup>[19]</sup>. Citation analysis involves ranking and evaluating an article or journal based on the number of citations it receives<sup>[20,21]</sup>. To accomplish this, we used a free software program called VOSviewer, which can be used to create and display bibliometric maps. VOSviewer, unlike commonly used mapping applications such as SPSS and Pajek, emphasizes the graphical representation of statistical data<sup>[18]</sup>. The functionality of VOSviewer is particularly useful for showing extensive bibliometric maps in an easy-to-understand manner<sup>[19,21,22]</sup>.

The productivity of authors in the field of PTLD, as well as the distribution of annual publishing outputs among countries, institutions, and journals, were the main analytical focuses of this study. These analyses will give readers unique perspectives and valuable information to foster collaboration. To the best of our knowledge, there has been no research carried out to assess which works on the subject of PTLD have had the most impact. Through conducting this study, we could identify the body of research that has had the most significant impact in this field to date, which will allow us to have a deeper comprehension of the PTLD.

## **Material and methods**

## Data collection and retrieval methods

On 28 November 2022, a search of the literature was conducted in an effort to minimize the adjustments to the number of citations while the search was being conducted. We have queried the Web of Science database using the terms ""PTLD" OR "Post-transplant lymphoproliferative disorder" OR "Post-transplant lymphoproliferative disease" whether they have appeared in the title and or abstract. The exact algorithm was "PTLD" OR "POST-TRANSPLANT LYMPHOPROLYFERATIVE DISORDER" OR "POSTTRANSPLANT LYMPHOPROLYFERATIVE DIS-ORDER OR "POSTTRANSPLANT LYMPHOPROLYFERATIVE DISEASE". The Web of Science Core Collection was chosen over

## HIGHLIGHTS

- This bibliometric study provides a comprehensive overview of global research productivity on post-transplant lymphoproliferative disorder (PTLD) from 2000 to 2021, including 1809 studies.
- The research output on PTLD has shown a notable incremental trend until 2011, with a second wave starting in 2017 and peaking in 2021, which had the highest number of publications (n = 124) and citations (3640 times).
- The United States is the leading contributor to PTLD research, producing 41.3% of the field's overall research output, followed by Germany, the United Kingdom, and Japan.
- The University of Pittsburgh, Harvard University, and the Medical College of Wisconsin are the top contributing institutions based on the citations of the articles.
- The most frequently cited authors in PTLD research are Sullivan KM, and Deeg HJ from the Division of Cancer Epidemiology at the National Cancer Institute, Bethesda, MD.
- The majority of articles were published in Pediatric Transplantation, Transplantation, and the American Journal of Transplantation.
- The most recurrent keywords in PTLD research are Ebstien-Barr virus, immunosuppression, and Rituximab, indicating the hot topics in the field.
- The most-cited article is "PD-L1 Expression Is Characteristic of a Subset of Aggressive B-cell Lymphomas and Virus-Associated Malignancies" by Chen, Benjamin *et al.*, published in Clinical Cancer Research in 2013.
- The study identifies the need for further research into the origin, pathogenic processes, and the role of oncogenic viruses in PTLD, given its high lifetime risk in the post-transplant population and the low overall survival rate.
- Future trends in PTLD research are predicted to focus on prevention, early detection, and treatment.

other databases due to its citation indexing and comprehensive coverage of high-quality, peer-reviewed scientific literature, especially in the medical and health sciences fields. This database stands out for its accurate reflection of the research landscape in PTLD, providing deeper insights through its robust citation network. This capability is essential for a nuanced bibliometric analysis, ensuring a more precise evaluation of research trends, key authors, and influential papers compared to other databases which may have a narrower scope or less rigorous citation tracking.

We extracted data including the title, author, institution, journal, year of publication, total citations, and the type of study. Moreover, "Full record and cited references" were downloaded, and raw data were transformed into TXT format, which allowed for the analysis of bibliometric tools. The inclusion criteria for enroled research for these studies is when the object of study is PTLD. Study designs included: case series, prospective cohort, randomized control trial, retrospective cohort, retrospective casecontrol, cross-sectional, case reports, and literature review. Exclusion criteria: Non-academic paper type data included: meeting abstract, editorial material, news item, letters, proceedings paper, book chapter, and correction.

This research did not involve animal experiments or clinical trials; thus, permission from an ethical committee was not required. There were no language limitations imposed. We have chosen the time period 2000–2022.

#### Data analysis

All analysis was based on the number of citations. We have analyzed annual trends, research productivity, and citations of countries, institutions, authors, journals, keywords, and articles. Tables and figures were generated using VOSviewer version 1.6.18 and MS Excel from Office 365. We have used a flow chart to elaborate on our included/excluded results.

We chose the most occurring keywords by limiting the minimum number of occurrences to 10; we got 84 keywords that met the criteria. In the keyword analysis, we manually removed words that implied the topic's title, "PTLD" or "post-transplant lymphoproliferative disorder" We also removed words related to the country of origin of the articles and redundant words and repeated words. We have analyzed the annual trends by examining the number of publications each year and the number of citations for all the documents. Citation count ranked the ten most-cited articles in each of the years from 2000 to 2022.

## Results

## Included studies

Out of 2814 search results, we have included 1809 studies. 216 of which were reviews, and 1593 were articles. The exclusion criteria omitted studies collected through meeting abstracts, letters, book chapters, and studies published before 2000 (n = 1005). Figure 1.

#### Analysis of annual trends

Figure 2. depicts the annual number of citations and publications since 2000. The total number of citations was 45 239 and 29 709 without self-citations with a mean of 25.01 citation per article.



There was a notable incremental trend towards the years until 2011, although the number of publications declined slightly between 2008 and 2009, then continue to decrease until the second wave that started in 2017 to reach the top in 2021. The year 2021 had the highest number of publications (n = 124) and highest number of citations with 3640 times, followed by 2020 with 120 publications and 3405 citations.

#### Distribution and contribution of countries and institutions

The majority of the 74 countries that published research on PTLD were European. The United States, Germany, the United Kingdom, Japan, France, and Italy published the most articles. The United States was, however, the source of the bulk of publications (n = 747) and citations (n = 25 740). The United States produces 41.3% of the field's overall research output, followed by Germany with 170 publications and 5679 citations, which contributes 9.4%, and the United Kingdom with 127 publications and 4233 citations, which contributes 7%, and Japan with 120 articles and 1069 citations. The country with the highest linkage strength was the USA (total link strength 158), followed by Germany (total link strength 121), France (total link strength 107), England (total link strength 79) then Switzerland (total link strength 76). Figure 3 depicts the visualization of each country's contribution and its relationships.

The bulk of the top 10 contributing institutions, based on the citations of the articles, were all located in the United States of America. The University of Pittsburgh topped the list with 64 articles and a total of 2700 citations, followed by Harvard University with 31 articles and 2189 citations, and the medical college of Wisconsin with 21 publications and 1682 citations. The University of Minnesota and the University of Pennsylvania had 26 and 34 articles, respectively, with 1675 and 1597 citations. Figure 4.

## Analysis of authors

Among all authors found in the query, 113 authors participated in at least five documents about PTLD, 61 participated in at least six articles, and 13 authors participated in at least ten articles. The top 10 most-cited authors are listed in Table 1. The top five authors with the highest citation were Sullivan KM, and Deeg HJ from the Division of Cancer Epidemiology at the National Cancer Institute, Bethesda, MD, with 950 and 895 citations, respectively. Reinke, Petra from Berlin Institute of Health, Berlin, Germany, with 847 citations, followed by Nalesnik, Ma from the Department of Pathology, University of Pittsburgh Medical Center, PA, and Riess, Hanno from the Department of Haematology and Oncology, University Medical Center Berlin, Germany with 816 and 814, respectively.

#### Analysis of journals of publication

Sixty-three journals have published at least five articles, 27 journals have published at least ten articles, and 19 journals have published at least 15 articles; however, there are only three journals that have published 50 or more articles on the topic of PTLD.

The majority of articles were published in Pediatric Transplantation (n = 147), Transplantation (n = 124), and the American Journal of Transplantation (n = 98). However, in terms of the number of citations, Transplantation has received the



Figure 2. Post-transplant lymphoproliferative disease publication trends from 2000 to 2022, the y-axis refers to the number of documents per year on the right, and the number of citations on the left.

highest number with 6499, followed by the American Journal of Transplantation with 5958, blood with 4107, and Pediatric Transplantation with 2143. The density network visualization map of the most-cited journals is shown in Fig. 5.

# Analysis of keywords

We have compiled a list of the ten keywords with the highest recurrence, which can be seen in Fig. 6. Ebstien-Barr virus was the keyword that appeared most commonly 398 times and as EBV 149 times, followed by immunosuppression (n = 144) and Rituximab (n = 142).

# Top-cited articles

The article entitled "PD-L1 Expression Is Characteristic of a Subset of Aggressive B-cell Lymphomas and Virus-Associated Malignancies" conducted by Chen, Benjamin *et al.* from Harvard



Figure 3. A network map showing most-cited countries involved in post-transplant lymphoproliferative disease research.



Figure 4. A network map showing most-cited institutions involved in post-transplant lymphoproliferative disease research.

University and published in the clinical cancer research journal in 2013, received the highest count of citations (585) with 58.5 citations per year on average. Followed by "Allogeneic cytotoxic T-cell therapy for EBV-positive post transplantation lymphoproliferative disease: results of a phase 2 multicenter clinical trial", conducted by Haque, Tanzina *et al.* from the University of Edinburgh and published in the Blood in 2007, received 441 citations with an average of 27.56 citations per year.

The article "A Phase III Study of Belatacept Versus Cyclosporine in Kidney Transplants from Extended Criteria

The top 10 cited au	ed authors involved in PTLD research			
Author	Citations	Total link strength		
Sullivan KM	950	380		
Deeg HJ	895	385		
Reinke Petra	847	2218		
Nalesnik MA	816	845		
Riess Hanno	814	2467		
Fung J	804	729		
Habermann TM	786	1183		
Curtis RE	768	349		
Horowitz MM	768	349		
Kingma DW	768	349		

PTLD,post-transplant lymphoproliferative disease.

Donors (BENEFIT-EXT Study)," which was done by Durrbach *et al.* from Paris-Sud University and published in the American Journal of Transplantation received 386 citations with 29.7 average citations per year. Then "Post-transplant lymphoproliferative disorders" article, which was done by Gottschalk A *et al.* and published in the annual review of medicine in 2005 with 308 citations and 17.11 average citations per year. The top ten most-cited PTLD articles are listed in Table 2.

#### Discussion

PTLD is one of the most serious complications of transplantation and is a consequence of therapeutic immunosuppression<sup>[23]</sup>. New insights into the biology of PTLD and the role of EBV infection, improvements in immunosuppressive strategies for transplantation, advances in the treatment of PTLD, and the application of new molecular-genomic techniques have led to more sophisticated diagnostic and therapeutic approaches that are improving outcomes for patients with PTLD<sup>[10,23,24]</sup>. However, there is much to be improved, explored, and learned. The current study aims to offer a thorough overview of the state of PTLD research globally and identify trends in its subsequent development.

PTLD have been identified for decades, but their origin, pathogenic processes, and the role of oncogenic viruses are just recently being unravelled<sup>[23,25]</sup>. A better knowledge of this disease is desperately needed because of the high lifetime risk in the



Figure 5. A network map showing most-cited academic Journals publishing research on post-transplant lymphoproliferative disease research.

post-transplant population and the low overall survival rate. We think it could be interesting to monitor the progression of PTLD by providing a global perspective on the research surrounding it and evaluating the relevance of articles published on the subject. However, to the best of our knowledge, no published literature on Bibliometric analyses specifically focused on PTLD. An insight into the distribution of publications and citations among nations, organizations, authors, and journals is provided by this bibliometric analysis, which compiled 1809 articles that were deemed significant and included in the analysis.

Bibliometric analysis is practical for understanding and mapping the accumulated scientific knowledge and evolutionary subtleties of well-established fields in a way that is easy to understand<sup>[20,21]</sup>. Consequently, well-executed bibliometric studies can lay the groundwork for advancing a field in novel ways; they enable and empower scholars to gain a comprehensive overview, identify knowledge gaps, generate novel research ideas, and position their intended contributions to the field<sup>[20]</sup>. In recent years, bibliometric tools like Gephi, Leximancer, and VOSviewer, together with scientific databases such as Scopus and Web of Science, have contributed to the rise in popularity of bibliometric analysis in medical research<sup>[26,27]</sup>. Scholars use bibliometric analysis to identify articles and journals' performance, collaboration patterns, and research components and investigate a particular area's intellectual structure in published literature<sup>[27]</sup>. The bibliometric analysis relies on large amounts of objective data, such as citations, publications, keywords, and subjects<sup>[22]</sup>.

This publication presents the most recent data from analyzing the most frequently cited works in the PTLD area. we observed a substantial increase in the number of publications and citations over the years, particularly from 2017 to 2021, indicating a growing academic interest and evolving understanding in this field. The dominant contribution from countries like the United States, Germany, and the United Kingdom, coupled with significant inputs from institutions such as the University of



Figure 6. Most occurrence key words visualization. Each circle represents a keyword, and the size of the circles represents the frequency of occurrence. Larger circles indicate that the keyword appears more frequently. Keywords included in the same cluster are displayed in the same colour. The distance between the two circles shows the degree of the relationship.

Pittsburgh and Harvard University, underscores the geographical and academic centres driving PTLD research. It is the first global analysis of the history and current status of PTLD research to evaluate the performance of leading countries and researchers, institutes, and research centres for this disease. Knowledge maps of PTLD were created using the VOSviower software to fully display the collaboration network in representative nations and institutions and offer a practical and adaptable method of identification and tracking.

In the early 1990s, the annual number of publications on the topic of PTLD was quite low, but in 2000 there was a peak of 47 publications, which marked the beginning of an increase in the number of publications. With 81 publications in 2007, the number of published documents reached an all-time high. Although the number of papers published decreased from 2007 to 2009, a new publication peak occurred in 2011 with 93 publications; the highest number of publications was recorded in 2021 and reached the third publication peak with 124 publications, indicating that the discussion on PTLD in transplantation in the last few years has once again attracted more attention and entered a period of rapid development. This increase can be attributed to a growth in the number of transplants, older donors and recipients, new immunosuppressive drugs, higher awareness, and enhanced diagnostic capabilities<sup>[4,8]</sup>.

The majority of research articles originated in North America and Europe, with the exception of Japan and China, which were among the top 10 Asian countries. Among the countries that have published on this subject, the United States stands out as the leader with 747 papers and 25 740 citations. Moreover, all of the top 10 most-cited institutions were located in the United States. This trend of increasing research output and the concentration of work in specific regions and institutions suggest potential areas for future collaboration and research focus, particularly in advancing diagnostic methods and therapeutic strategies for PTLD.

As evidenced by the considerable amount of literature on the subject, PTLD after kidney transplantation appears to garner the most interest among researchers. We retrieved 819 articles out of 1809 when we restricted our search to those that specifically addressed PTLD in the kidney transplant population. Furthermore, Table 2 shows that two of the top 10 articles on the PTLD that have received the most citations are about PTLD following kidney transplantation.

As the risk of PTLD among solid organ recipients is estimated to be three to twenty-one times that of the general population and possibly as much as one hundred twenty times greater among children who receive SOT<sup>[7,28,29]</sup>, it is not surprising that the journal with the most publications on this subject is paediatric transplantation, with 147 articles. Keywords are a specially formulated form of research content and a significant indicator that represents the research topic and hotspots. The most often occurring keywords were EBV, rituximab, and immunosuppression, which may provide insight into the hottest themes in PTLD research, namely the importance of EBV in the pathophysiology of the disease and the involvement of immunosuppression in triggering PTLD. Moreover, the findings

Authors	Year	Title	Source title	Cited by
Chen BJ	2013	PD-L1 Expression Is Characteristic of a Subset of Aggressive B-cell Lymphomas and Virus-Associated Malignancies	Clinical Cancer Research	585
Haque T	2007	Allogeneic cytotoxic T-cell therapy for EBV-positive posttransplantation lymphoproliferative disease: results of a phase 2 multicenter clinical trial	Blood	441
Jurrbach A	2010	A Phase III Study of Belatacept Versus Cyclosporine in Kidney Transplants from Extended Criteria Donors (BENEHT-EXT Study)	American Journal of Transplantation	386
Choquet S	2006	Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disordens: results of a prospective multicenter phase 2 study	Blood	299
Caillard S	2005	Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modem immunosuppression	Transplantation	298
enn l	2000	Post-transplant malignancy - The role of immunosuppression	Drug Safety	293
Taylor AL	2005	Post-transplant lymphoprolifierative disorders (PTLD) after solid organ transplantation	Critical Reviews in Oncology Hematology	271
Haque T	2002	Treatment of Epstein-Barr-virus-positive post-transplantation lymphoproliferative disease with partly HLA-matched allogenetic cytotoxic T cells	Lancet	266
-andgren 0	2009	Risk factors for lymphoproliferative disorders after allogeneic hematopoietic cell transplantation	Blood	260
socie G	2000	New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia	Joumal of Clinical Oncology	250

demonstrated that "kidney transplantation, liver transplantation, and pediatric" were extremely central areas of focus of the PTLD research.

Despite some recent advances in PTLD research, the field continues to face a number of challenges in its search for a new classification<sup>[20]</sup>, the development of novel therapeutic targets to mitigate PTLD's detrimental consequences, and the development of vaccine therapy for patients at risk for PTLD prior to organ transplantation<sup>[27]</sup>. In the present study, knowledge maps of PTLD were created using the VOSviower software to fully display the collaboration network in representative countries and institutions and to offer a practical and adaptable method of identification and tracking.

This study has several limitations. We started our search using only the WoSCC database. We did not use multiple search engines (e.g. Scopus, Ovid, PubMed, Google Scholar). Second, the number of citations is an indirect metric of scientific impact that may be affected by other factors, such as journal accessibility and reputation. Finally, because the number of research is expanding rapidly, it is anticipated that the list of the most-cited articles will change over time.

# Conclusion

With ongoing debates over optimal classification, EBV involvement, and treatment, this topic has received significant interest from researchers in recent years. As a result, the number of publications has increased significantly over the past two decades. The United States has produced the vast majority of PTLDrelated articles, and transplantation journals are the most frequently cited. For PTLD after solid organ transplantation, we have listed the following two hot topics: EBV and Immunosuppression are the most researched areas. We predict that future trends in PTLD research will focus a greater emphasis on prevention and early detection and treatment.

## **Ethical approval**

It's a review article, no ethical approval required.

## Consent

It's a review article, no consent required.

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Not applicable.

## Author contribution

All authors have made substantial contributions to the conception and design of the study, or acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be submitted.

## **Conflicts of interest disclosure**

There are no conflicts of interest.

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#### Guarantor

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#### Data availability statement

Data are available upon request.

#### **Provenance and peer review**

Not applicable.

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