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Grading Histopathology Features of Graft-versus-host Disease in Animal Models: A Systematic Review

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ABSTRACT

Graft-versus-host disease (GvHD), a frequent and severe complication following allogeneic hematopoietic stem cell transplantation, presents substantial morbidity and mortality risks. The crucial role of histopathological examination in diagnosing and grading GvHD, particularly within animal models, is pivotal for elucidating disease mechanisms and assessing emerging therapies. This systematic review aims to critically evaluate the various grading systems for GvHD in animal models, emphasizing histopathological characteristics. In this endeavor, we meticulously examined original research articles sourced from PubMed, Scopus, Web of Science, and Google Scholar. Our findings reveal a diverse array of grading systems, each differing in the tissues examined, criteria evaluated, severity scoring scales, and the granularity of the information provided. Predominantly, skin, liver, and gut tissues are assessed, though some systems also incorporate lung and thymus evaluations. This review will delve into the alignment between clinical and histological grading in animal models of GvHD, also casting light on prospective advancements and the impact of technological progress. In conclusion, our analysis underscores the imperative need for uniform criteria and consistent application of grading systems. Such standardization is essential to foster comparability across studies and enhance the translation of preclinical discoveries into clinical applications.

Keywords Animal model; Grading system; Graft-versus-host disease; GvHD; Histopathology

INTRODUCTION

Graft-versus-host disease (GvHD) is a multifaceted complication that may develop following allogeneic hematopoietic stem cell transplantation (HSCT). GvHD occurs when the donor's immune cells recognize the host's cells as foreign, leading to an immune reaction affecting multiple organ systems, including the skin, liver, and gastrointestinal tract.[1-3]

The general incidence of GvHD is estimated to be 40% in patients receiving sibling donor transplants and in patients receiving unrelated donor transplants is up to 60%.[4]

Despite recent developments to decrease the prevalence of GvHD through changing prophylactic regimens and decreasing the severity of conditioning before transplantation, useful and practical treatments for GvHD are insufficient. Therefore, it is important to have reliable and precise experimental models of GvHD

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are vital to advance our basic knowledge of this disorder and developing novel treatments.[5]

Moreover, patients with acute or chronic GvHD who do not respond to corticosteroids have raised rates of morbidity and mortality related to intense immune suppression and/or end-organ damage from the progression of GvHD. Although many clinical studies assess treatment interventions, there are few approved therapeutic approaches for GvHD.[6]

Over the past few decades, to improve the outcome of patients suffering from GvHD, or even inhibit its occurrence, many preclinical studies have concentrated on this disease. Animal models are commonly used to study the pathogenesis and treatment of GvHD. The evaluation of GvHD severity and progression in animal models is crucial to developing better therapies and interventions.[7]

Current methodologies involve histopathological grading systems that assess tissue damage and cellular infiltration in affected organs. Grading is significant in evaluating the response to prophylaxis or treatment and its effect on survival. However, the complexity of GvHD's pathophysiology and the variability in grading systems necessitates a more nuanced and systematic understanding.[5]

MATERIALS AND METHODS

The protocol of the study was published and publicly available on the internet and via the link: https://www.researchgate.net/publication/376894645_Animal_review_Protocol_title_Grading_Histopathology_Features_of_Graft-versus-host_disease_in_Animal_Models_a_Systematic_Review

We conducted a comprehensive literature search in electronic databases, including PubMed, Web of Science, Google Scholar, and Scopus, up to April 2023. The eligibility criteria were:

1. Original articles that focused on grading histopathology features of GvHD in animal models,
2. Studies published in English,
3. Studies that utilized peer-reviewed methodologies.

Search strategy:

Our search strategy included using the following keywords for this systematic review: "graft-versus-host disease", "GvHD", "animal model", "histopathology", and "grading system".

- The determined search terms for each keyword were:

"graft-versus-host disease" OR "GvHD"

"animal model" OR "animal study" OR "animal experiment"

"histopathology" OR "tissue pathology" OR "histology"

"grading system" OR "severity scoring" OR "scoring system"

We combined these search terms using Boolean operators to search for relevant articles on PubMed, Scopus, Web of Science, and Google Scholar for relevant articles.

Then we screened the titles and abstracts of the articles to identify relevant studies for inclusion in the systematic review.

The Systematic Review Centre for Laboratory Animal Experiments (SYRCLE) tool was used to assess and report potential bias in the animal studies included in this review.[8]

RESULTS

Our search yielded a total of 150 articles. After a detailed evaluation process, six articles were included in this review (Figure 1)

We applied the SYRCLE tool to evaluate the risk of bias in this pre-clinical animal study [8] (Table 1). Baseline characteristics of mice were stated for four of the six studies. Only one of the studies stated the initial number of mice who received transplants, and neither of the studies revealed sample size calculations. Random allocation of animals in control and experimental groups was only defined for two of the six studies. Also, two of the studies described blinding through randomization or outcome assessments. It was not obvious that there was an attrition bias in any of the studies and none of the treated animals were included in the ultimate assessment. Table 1 outlines the assigned risk of bias in each of the statements for some of the main studies included in our analysis.

The Importance of Animal Models in Understanding GvHD

Animal models, particularly murine models, have been instrumental in understanding the pathogenesis and progression of GvHD.[7] The homology between murine and human immune systems has provided significant

insights into the immune response, enabling the development of potential therapeutic interventions.[9]

Historical Histopathological Grading Systems

Different historical histopathological grading systems for GvHD in animal models are discussed in the following (Table 2).

Cooke-Kruskall Grading System

The Cooke-Kruskall grading system is one of the earlier histopathological grading systems that was developed to evaluate GvHD in animal models. It focuses on two parameters; cellular infiltration and epithelial damage, that are crucial for the manifestation of GvHD.[10]

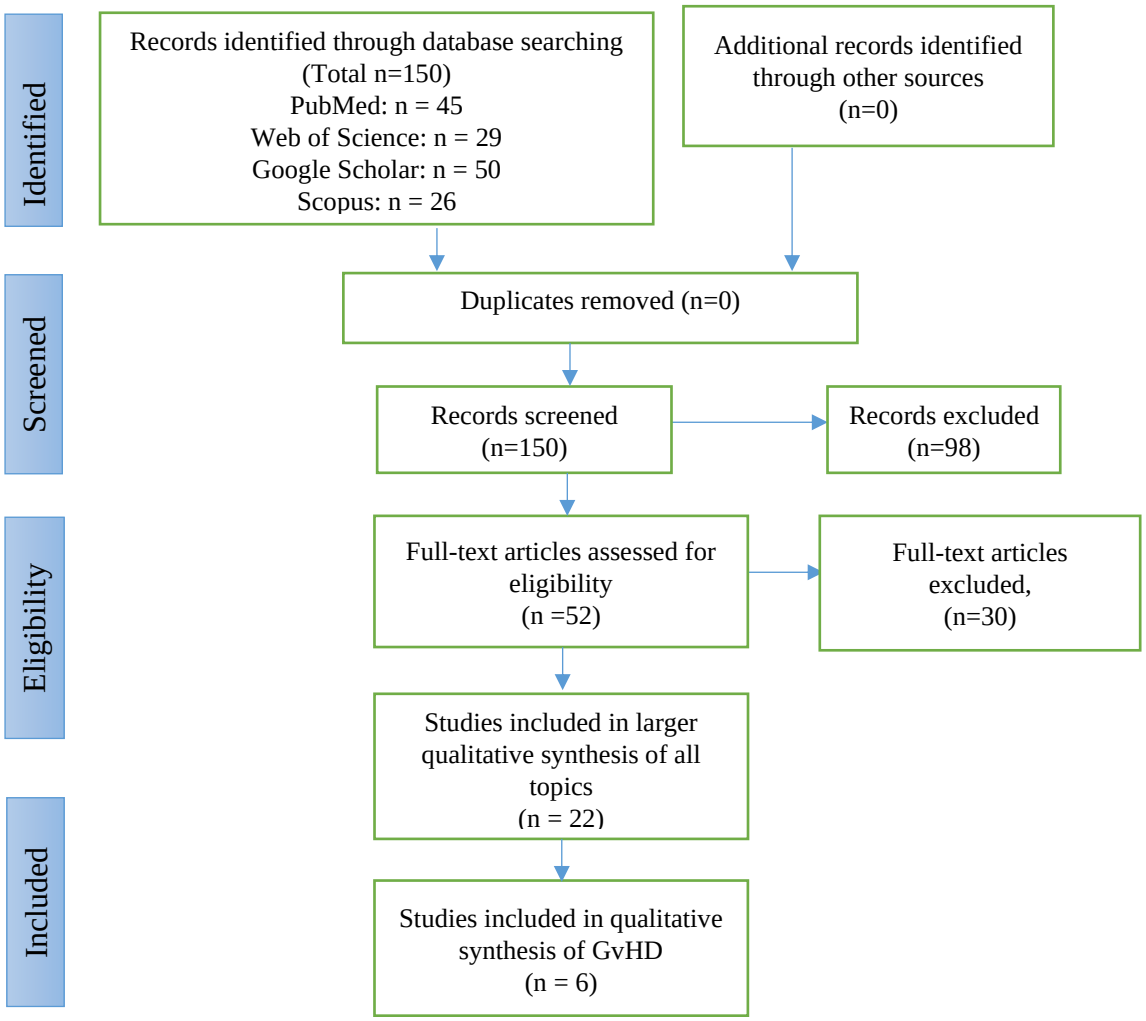

Figure 1. PRISMA diagram outlining the identification of articles included in the analysis

Table 1. Risk of bias applying SYRCLE tool for preclinical studies. Unclear risk of bias (grey circles), Low risk (open circles), and high risk (black circles), are illustrated for each study.

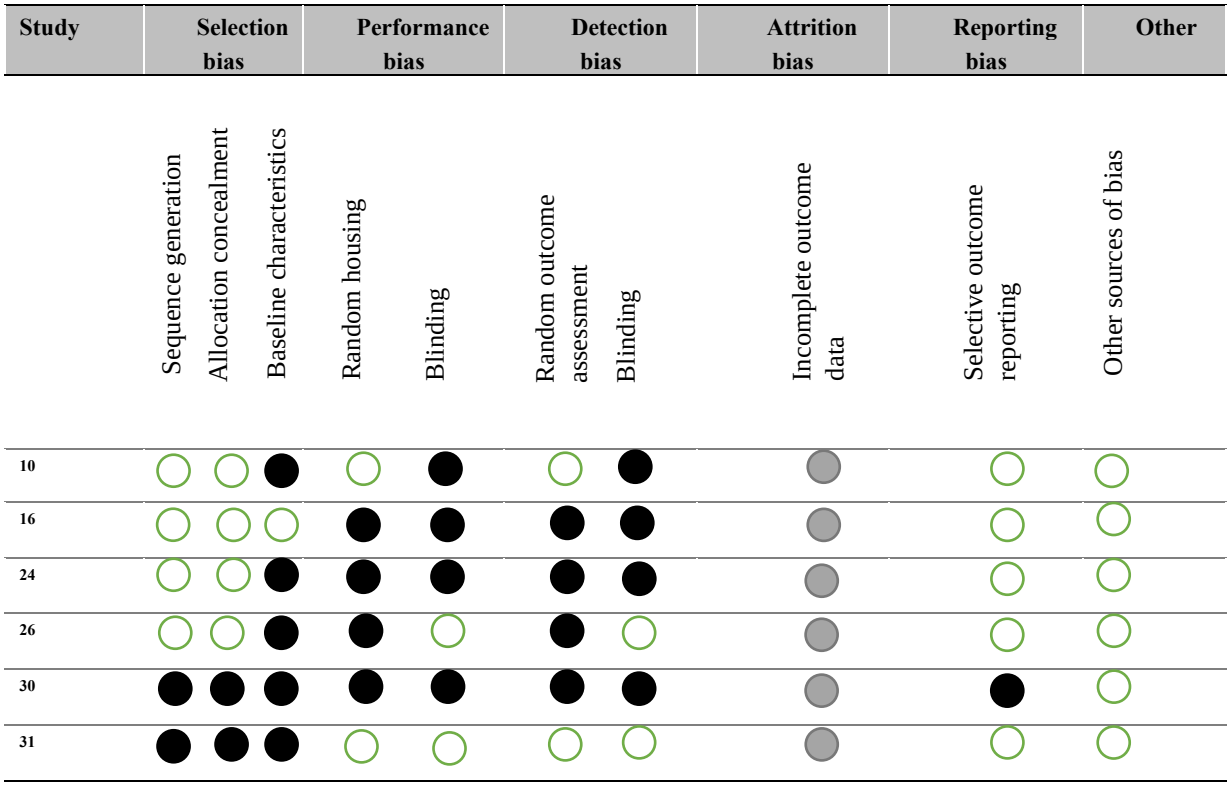

Table 2. Summarizing important grading systems for GvHD in animal models. These grading systems provide important tools for evaluating the severity and progression of GvHD in preclinical studies.

grading system	organs evaluated	complexity	clinical parameters	histopathological parameters	focus
cooke scoring system	Liver, lung, and GI tract	Low	No	Cellular infiltration, epithelial damage	Cellular changes
lerner	liver, skin, and small intestine	Medium	No	Cellular infiltration, epithelial damage, organ-specific changes	Organ-specific changes
hill scoring system	Skin, liver, and GI tract	Medium	No	Apoptotic bodies in the gastrointestinal tract	Apoptosis
ferrara scoring system	Liver, lung, and GI tract	Medium	Yes (Skin, liver, and gut involvement)	No	Clinical parameters and organ involvement
socié and blazar	skin, liver, and GI tract	High	Yes (weight loss, fur texture, posture, activity, skin integrity	Cellular infiltration, epithelial damage, apoptotic bodies, organ-specific changes	Integrative approach
shlomchik scoring system	Skin, liver, and GI tract	High	Yes (weight loss, fur texture, posture, activity, skin integrity	Cellular infiltration, epithelial damage, apoptotic bodies, organ-specific changes	Integrative approach

Note: This table is not exhaustive and other grading systems have been developed and utilized in animal models of GvHD.

In the Cooke-Kruskall grading system, each tissue sample is evaluated for cellular infiltration and epithelial damage under a microscope. Cellular infiltration is determined by the number of lymphocytes present in the tissue sample that indicates an immune response. Epithelial damage, on the other hand, is evaluated based on changes in the structure of the epithelial tissue, including cell death, disruption of the normal tissue architecture, and fibrosis.

One of the key strengths of the Cooke-Kruskall system lies in its simplicity and ease of interpretation. It allows for straightforward comparisons across different studies and facilitates a quick understanding of the severity and progression of GvHD. Its wide use has allowed for some level of standardization in the research field.

However, the Cooke-Kruskall grading system also has its limitations. It lacks the sensitivity to differentiate between the different stages of GvHD, especially in more complex and severe cases. For example, it might not accurately differentiate between moderate and severe GvHD, as it does not incorporate a range of histopathological changes seen in these conditions.

Moreover, the system does not account for organ-specific differences in the manifestation of GvHD. This aspect has been identified as an important consideration in GvHD research, considering the disease's systemic nature and the fact that it can affect multiple organs differently.

Lerner Grading System

The Lerner Grading System represents an evolution in the histopathological grading of GvHD, shifting the focus from solely examining cellular infiltration and epithelial damage to a more organ-specific evaluation.[11]

The Lerner grading system scores histopathological changes in the liver, skin, and small intestine individually, acknowledging the fact that GvHD can have varying manifestations across different organ systems. Each organ is graded from 0 to 4 based on the severity of histopathological changes.

For the skin, the system takes into account epidermal changes such as spongiosis, vacuolization, and the presence of apoptotic bodies, with higher scores indicating more severe damage. The liver is evaluated for signs of cholangitis, bile duct necrosis, and parenchymal infiltration, while the small intestine is assessed for signs of villous blunting, crypt cell apoptosis, and transmural infiltration.

One of the significant benefits of this system is that it increases sensitivity by assessing GvHD symptoms at an organ-specific level. This approach recognizes the systemic nature of GvHD and the varying degrees of involvement it can have across different organ systems.

However, the Lerner grading system also comes with its set of limitations. It requires a more intensive and time-consuming examination of histopathological samples, as three different organ systems need to be evaluated separately. Additionally, the system does not incorporate some clinical parameters that may be reflective of GvHD severity.

Hill Grading System

The Hill Grading System was proposed by Hill and colleagues in 2000 and marked a significant evolution in the histopathological grading of GvHD by focusing on the count of apoptotic bodies, particularly in the gastrointestinal tract.[12] This focus on apoptosis represents an important shift from previous grading systems, which primarily concentrated on cellular infiltration and epithelial damage.

In the Hill grading system, tissue samples from the gastrointestinal tract are examined under a microscope to count the number of apoptotic bodies per high-power field. The number of apoptotic bodies is then used to measure GvHD severity, with higher counts indicating more severe GvHD.

Apoptosis, or programmed cell death, is a critical parameter in GvHD's pathophysiology. It is believed that donor T cells induce apoptosis in host cells, causing tissue damage in GvHD. So, the Hill grading system provides a more specific understanding of the cellular changes occurring during GvHD.

However, the Hill grading system has its limitations. It emphasizes one particular organ system - in this case, the gastrointestinal tract - while GvHD is a systemic disease that affects multiple organ systems. Therefore, it may not fully capture the systemic severity of GvHD.

Moreover, the grading system is relatively complex and requires the precise counting of apoptotic bodies, which can be a time-consuming process and could also introduce potential observer variability.

Scoring System by Socié and Blazar

The scoring system proposed by Socié and Blazar in 2009 brought a significant advancement in the grading of GvHD in animal models, as it integrated histopathological evaluations with clinical parameters.[13] This system introduced a much-needed holistic approach toward the evaluation of GvHD.

In the Socié and Blazar scoring system, histopathological examination of various organs including the skin, liver, and gastrointestinal tract is performed, like the Lerner grading system. Each organ is evaluated separately for hallmarks of GvHD, such as cellular infiltration, epithelial damage, and the presence of apoptotic bodies. However, in addition to these histopathological changes, this system also takes into account clinical parameters such as weight loss, fur texture, posture, activity, and skin integrity. Each parameter is scored, and a final composite score is generated, which gives a comprehensive overview of the severity and impact of GvHD on the organism.

The inclusion of clinical parameters in this grading system is particularly valuable as it aligns more closely with the clinical reality of GvHD, which often presents as a systemic disease with a wide range of clinical symptoms. This holistic approach offers a more comprehensive understanding of the disease's impact on the overall organism, and this can be crucial in evaluating therapeutic interventions.

Despite its comprehensive nature, the scoring system by Socié and Blazar does have its limitations. It is considerably more complex and time-consuming compared to previous grading systems. The inclusion of multiple clinical parameters and the need to generate a composite score requires a substantial amount of data collection and analysis.

Organ-based Grading Histopathology Features

Histopathology has been recognized as an essential tool in diagnosing and staging GvHD.[14] The most common organs affected include the lungs, skin, liver, and gastrointestinal tract. The histopathological grading is based on the severity of inflammation, necrosis, and fibrosis[15] (Table 3 and 4).

Table 3. Grading systems for GvHD in animal models for five organs.

Organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Reference
SKIN	Normal	Mild vacuolar alteration of the basal layer, few apoptotic bodies	Moderate vacuolization, dyskeratosis, scattered apoptotic bodies	Widespread vacuolar alteration, increased apoptotic bodies, some necrosis of individual keratinocytes	Severe changes with necrosis, bulla formation, ulceration	11, 27
LIVER	Normal	Mild bile duct epithelial cell degeneration and apoptosis	Moderate cholestasis and periportal infiltration	Severe cholestasis, more extensive infiltration, bile duct degeneration	Bile duct loss, bridging necrosis, fibrosis	20, 33
LUNG	Normal	Minimal perivascular and peribronchiolar lymphocytic infiltration	Mild thickening of alveolar septa and bronchiolar epithelium	Moderate interstitial pneumonia, alveolar exudates	Severe obliterative bronchiolitis, extensive fibrosis	17, 18, 34
Gi Tract	No change	Mild crypt cell degeneration and apoptosis	Crypt loss (<50%) and mild mucosal inflammation	Crypt loss (>50%) with moderate inflammation	Crypt loss with severe mucosal ulceration and transmural inflammation	16, 21, 35
SPLEEN	No change	Mild lymphoid hyperplasia and sinusoidal inflammation	Moderate lymphoid hyperplasia, more prominent sinusoidal inflammation	Marked lymphoid hyperplasia, significant sinusoidal inflammation	Severe changes including extensive lymphoid hyperplasia and sinusoidal inflammation	22, 23

These grades are provided in a simplified format for better understanding, the exact criteria can differ based on the specific experimental conditions and animal models.

Table 4. The relationship between the histopathology features of GvHD and clinical signs and symptoms in animal models

Organ/Tissue	Clinical Signs/Symptoms	Histopathology Features	References
Skin	Erythema, scaling, alopecia	Epidermal hyperplasia, dyskeratosis, lymphocytic infiltration	11, 26
Gastrointestinal (Gi) Tract	Diarrhea, anorexia	Crypt apoptosis, mucosal denudation, lymphocytic infiltration	16, 27
Lung	Respiratory distress	Bronchiolar inflammation and fibrosis	17, 28
Liver	Jaundice	Bile duct damage, lymphocytic infiltration	20
Spleen	Enlargement (not easily observable in small animals)	Lymphoid hyperplasia, sinusoidal inflammation	22, 23

As noted in the table, the severity of the clinical signs and symptoms in animal models often aligns with the histopathological grading, which can aid in predicting disease progression and response to therapy. It is important to remember that both clinical and histopathological assessments have their advantages and limitations, and using them together can provide the most comprehensive understanding of GvHD.

Lung GvHD

Lung involvement in GvHD typically manifests as bronchiolitis obliterans syndrome.[16] Histological examination reveals obliteration of bronchioles by inflammation and fibrosis.[17] Grading ranges from 0 (no obliterative bronchiolitis) to 4 (severe obliterative bronchiolitis with extensive fibrosis).[18]

Skin GvHD

Histopathological manifestations of skin GvHD include basal cell degeneration, apoptotic keratinocytes, and infiltration of lymphocytes.[11] The grading of skin GvHD ranges from grade 0 (no change) to grade 4 (severe changes, such as extensive epidermal necrosis).

Liver GvHD

Liver involvement is common in GvHD. Histological features include portal inflammation, bile duct damage, endothelialitis, and fibrosis.[19] The grading system ranges from 0 (no change) to 4 (severe changes including bile duct loss and severe fibrosis).[20]

Gastrointestinal GvHD

Histopathological features in gastrointestinal GvHD include crypt apoptosis, mucosal denudation, loss of glandular structures, and infiltration of lymphocytes.[16] The grading system ranges from 0 (no change) to 4 (severe changes including mucosal ulceration and transmural lymphocytic infiltration).[21]

Spleen GvHD

Spleen involvement in GvHD is characterized by lymphoid hyperplasia and sinusoidal inflammation.[22] The grading of spleen GvHD ranges from 0 (no change) to 4 (severe changes including extensive lymphoid hyperplasia and sinusoidal inflammation).[23]

DISCUSSION

Inter-observer Variability in Grading Histopathological Features

A significant challenge in histopathological evaluation is inter-observer variability. To reduce this discrepancy, the NIH Consensus development project established the histological grading criteria for GvHD in 2014.[24] Future widely accepted and standardized systems in GvHD of animal models are needed particularly in more complicated models like NOG mice or humanized mice models.

The Interplay Between Histopathology Features and Clinical Signs and Symptoms of GvHD in Animal Models

Understanding the relationship between the histopathological features of GvHD and its clinical manifestations in animal models is essential for improving disease management and enhancing the predictive and therapeutic value of these models.

Clinical Signs and Their Histopathological Correlates

The clinical manifestations of GvHD in animal models, particularly murine ones, are remarkably similar to those in humans. These include weight loss, skin changes, diarrhea, and other systemic signs indicative of organ involvement.[25]

In the skin, clinical signs such as erythema, scaling, and alopecia are often associated with histopathological changes like epidermal hyperplasia, dyskeratosis, and infiltration of inflammatory cells.[11,26] The severity of these histological changes often correlates with the extent of the visible skin lesions.

Gastrointestinal involvement is clinically manifested by diarrhea and anorexia, reflecting underlying histopathological changes such as crypt apoptosis, mucosal denudation, and lymphocytic infiltration.[16,27] Severe mucosal damage often correlates with persistent and severe diarrhea.

Lung involvement can result in respiratory distress, correlated histologically with bronchiolar inflammation and fibrosis seen in BOS.[17,28] Liver involvement can lead to jaundice, correlating with histological signs of bile duct damage and lymphocytic infiltration.[20]

In each of these cases, the severity of clinical signs often aligns with the histopathological grading. This concurrence not only validates the grading system but also aids in predicting disease progression and response to therapy based on clinical signs alone.

The Value and Limitations of Clinical Signs

Clinical signs of GvHD in animal models provide a rapid, non-invasive way of monitoring disease progression and response to therapy. However, they may lack specificity and sensitivity, particularly in the early stages of the disease. Furthermore, some manifestations, such as weight loss, may be influenced by other factors, confounding their interpretability.[29]

Conversely, histopathological examination allows for a more precise GvHD assessment severity and progression. Nonetheless, it requires tissue samples, which can be challenging to obtain, particularly in small animal models.

Advances in Grading Histopathology Features

The incorporation of digital pathology and machine learning algorithms may further enhance the accuracy and reproducibility of histopathological grading.[30] Several studies have already shown promising results in grading GvHD using these technologies.[31,32]

Limitations and Future Directions

Though our systematic review covers a broad scope of current literature on grading histopathology features of GvHD in animal models, it is not without limitations. For instance, our search strategy was limited to articles written in English, which may exclude valuable insights from non-English studies. Furthermore, the wider inclusion range of animal models beyond murine ones would increase the applicability of our findings.

Furthermore, future research should seek to refine and enhance the precision of grading histopathology features of GvHD in animal models, in particular through technological advancements like digital pathology and machine learning. Additionally, the development of standardized histopathological grading criteria across different animal models will aid in improving the consistency and comparability of findings across studies. Furthermore, incorporating more diverse animal models will enhance our understanding of GvHD's complex pathogenesis and foster the development of new therapeutic strategies.

CONCLUSION

Histopathological grading is an essential component of understanding GvHD progression and treatment response. In animal models, these grading methods provide useful insights into the pathogenesis of the disease and serve as useful tools for evaluating therapeutic interventions. With the incorporation of technological advancements, such as digital pathology and machine learning, the accuracy and consistency of histopathological grading can be significantly enhanced, paving the way for the development of novel therapeutic strategies for managing GvHD. The evolution of histopathological grading in animal models promises to enhance our understanding of GvHD and inform the development of new treatment approaches.

The relationship between the histopathological features of GvHD and its clinical signs in animal models underpins the utility of these models in studying this complex disease. By offering complementary insights, these two aspects can help improve our understanding of GvHD and inform the development of therapeutic strategies. Further research should aim to explore the relationship between clinical signs and histopathological changes, and validate the former as surrogate markers of the latter.

STATEMENT OF ETHICS

No ethical concern

FUNDING

Not applicable

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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