Blood and Lymphatic Cancer: Targets and Therapy

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REVIEW

Natural Killer/T-Cell Lymphoma-Associated Hemophagocytic lymphohistiocytosis—a Rare and Dangerous Disease

Guangqiang Meng[1], Manzhi Wang[1], Congcong Sun[1], Gege Feng[2], Jing Ren[1], Saran Feng[1], Yan Wang[1]

[1]Department of Hematology, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Jinan, Shandong, People's Republic of China; [2]Department of Hematology, Qilu Hospital of Shandong University, Jinan, Shandong, People's Republic of China

Correspondence: Guangqiang Meng, Email menggq2001@163.com

Abstract: Hemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome characterised by the reactive activation of cytotoxic T-lymphocytes and macrophages along with a substantial amount of cytokine secretion caused by various inductions. Natural killer/T-cell lymphoma (NKTL)-associated HLH (NK/T-LAHLH) is rare in clinical practice with an incidence rate of 7.1–11.9% in NKTL patients. Currently, there is no standard first-line treatment with good efficacy for NK/T-LAHLH. The treatment of NK/T-LAHLH is still mainly based on chemotherapy regimens containing etoposide and dexamethasone. Recently, many new therapeutic drugs and schemes have been trialled for the treatment of NK/T-LAHLH, such as ruxolitinib, immune checkpoint inhibitors, pegaspargase, and the DEP regimen. However, NK/T-LAHLH is associated with overall poor prognosis. Improving overall understanding of NK/T-LAHLH is of great significance to ameliorating patient prognosis. This review systematically discussed the epidemiology, pathogenesis, clinical features, current treatment regimens, and prognosis of NK/T-LAHLH to comprehensively elucidate this disease.
Keywords: NK/T-cell lymphoma, hemophagocytic lymphohistiocytosis, pathogenesis, treatment regimens, prognosis

Background

Hemophagocytic lymphohistiocytosis (HLH) is a rare immune-mediated syndrome wherein cytotoxic T lymphocytes and the mononuclear macrophage system over-activate and oversecrete inflammatory cytokines, leading to multiple organ injuries.[1,2] The pathophysiological feature of HLH is hyper-inflammatory cytokinemia, and its main clinical and laboratory features include fever, hemocytopenia, hepatosplenomegaly, hyperferritin, organ injury, and coagulation dysfunction.[1,2] Depending on its aetiology, HLH can be divided into primary and secondary types. Primary HLH is a recessive genetic disease,[1,3] whereas secondary HLH's aetiology includes infections, malignant tumours and autoimmune diseases. Lymphoma is the common cause of secondary HLH.[4,5] In secondary lymphoma-based HLH, T-cell and NK/T-cell lymphoma (NKTL) are more common, and NKTL accounts for approximately 35% of cases.[6] NKTL-associated HLH (NK/T-LAHLH) typically exhibits rapid progression, impaired treatment response, and poor prognosis. This study aimed to synthesise recent studies on NK/T-LAHLH and provide an overview of its epidemiology, pathogenesis, diagnosis, current therapies, and prognostic factors.

Epidemiology of NK/T-LAHLH

NK/T-LAHLH incidence varies among studies. Regarding the increased prevalence of NKTL in Asia and Latin America, its main epidemiological data are derived from Asian studies. Moreover, NKTL is the predominant cause of lymphoma-triggered HLH in Asia[7,8] and is divided into nodal and extranodal NKTL (ENKTL). In Asia, North America, and Europe, ENKTL accounts for 22.4%, 5.1%, and 4.3% of peripheral T-cell and NKTL, respectively.[9] Thus, ENKTL-related HLH is the most common type of NK/T-LAHLH. According to studies on the Chinese population, NK/T-LAHLH incidence

https://doi.org/10.2147/BLCTT.S574445
Received: 15 October 2025
Accepted: 19 January 2026
Published: 27 January 2026

ranges from 7.1% to 57.1%.[10–15] In a study involving 202 patients with ENKTL, 11.4% had HLH, and Jia et al reported that in a 202 cohort of patients with ENKTL, HLH incidence was 11.4% (23/202).[11] In a retrospective study by Li et al, HLH occurred in 21 of 295 patients with ENKTL, with an incidence of 7.1%.[12] Wei et al revealed that of 363 patients with ENKTL, 43 developed HLH with an incidence rate of 11.9%.[13] Moreover, He et al discovered that HLH occurred in 108 of 1134 ENKTL cases, and that the incidence of NK/T-LAHLH was 9.5%.[14] In contrast, another study conducted by a large HLH centre in Beijing found that 57.1% of patients had HLH.[15] While, HLH incidence should increase in specialised centres, the substantial risk of underdiagnosis in studies that reported a relatively lower incidence could not be overlooked. Through previous large-sample studies reported, it was found that the incidence of NK/T-LAHLH was approximately 7.1–11.9%.[11–14] NK/T-LAHLH incidence has not been reported in large-scale case studies in Europe and North America.

Pathogenesis of NK/T-LAHLH

The specific pathogenesis of NK/T-LAHLH remains unclear at present. Several possible mechanisms have been suggested for its involvement in NK/T-LAHLH (Figure 1). Wen et al demonstrated an association between a mutation (c.419T>C) in the evolutionarily conserved signalling intermediate in the Toll pathway (ECSIT) gene and NK/T-LAHLH.[16] The variant triggers NF-κB pathway through increasing its binding with S100A8/S100A9 heterodimer, elevating the affinity of arachidonic acid to S100A9, promoting the assembly of NADPH oxidase as well as over-production of interferon gamma (IFN-γ) and tumour necrosis factor α (TNF-α), inducing macrophages and cytokine storm. However, in another multiple-cohort study, the researchers prompted a contrary view.[17] The ECSIT-T419 mutation was verified to be a germline mutation, as reported in previous studies, with no association to NK/T-LAHLH.[17] Therefore, additional studies are required to assess the role of the ECSIT-T419 variant in NK/T-LAHLH.

Studies have demonstrated the essential role of JAK3 and its related signalling in NKTL pathogenesis.[18–20] Picod et al reveal that constitutively activated JAK3 leads to the hypersecretion of IFN-γ through the increase of NK cells sensitivity to interleukin-2.[21] When transplanting JAK3^{A573V}-transduced bone marrow cells into a wild-type model, researchers observed an expansion of NK cells and the development of HLH in recipients.

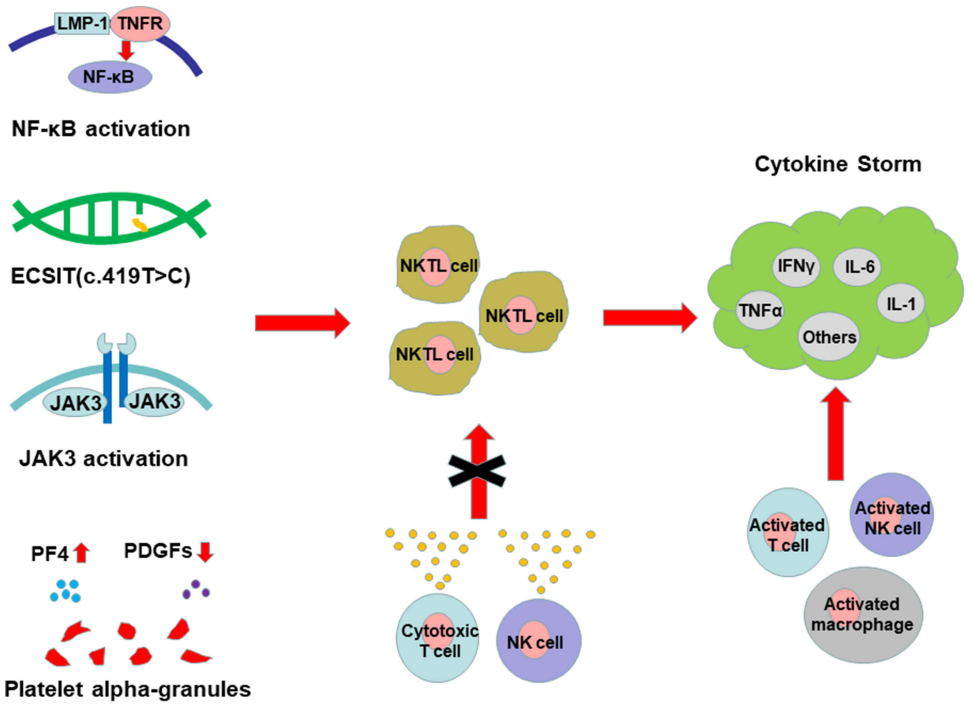

Figure 1 Pathogenesis diagram of NK/T-LAHLH.

Platelets are essential to this process, as the specific platelets produced in patients with NK/T-LAHLH releasing alpha-granules containing upregulated platelet factor 4 (PF4) and reducing platelet-derived growth factor (PDGFs), ultimately contributing to inflammation overactivation.[22]

Epstein–Barr virus (EBV), a DNA virus belonging to the genus Lymphocytophilus in the Herpesviridae family, which drives the development of primary HLH and participates in lymphoma-related HLH.[23–28] Moreover, EBV is present in >90% of NKTL cases. Several studies have attempted to elucidate the mechanism whereby EBV triggers T-cell lymphoma-associated HLH. When infecting T cells, EBV expresses latent membrane protein 1 (LMP-1) and induces TNFR-associated factor/NF-κB/ERK signalling to promote cytokine secretion.[29,30] Additionally, the activated NF-κB signalling protects the infected T cells from TNF-α-induced apoptosis. In another study, the localisation of EBV infection had highly significant effects on patient prognosis. In PTCL, patients with T-cell infection have a worse prognosis than those with B-EBV, as EBV exclusively localises to B cells and is correlated with a low incidence of HLH.[31]

Clinical Characteristic and Risk Factors of NK/T-LAHLH

NK/T-LAHLH diagnosis relies on the criteria for both NKTL and HLH, of which the most widely accepted criteria for HLH are the HLH-2004 revised by the International Histopathological Society.[32] Owing to the similarities between the clinical symptoms of NKTL and HLH, diagnosing lymphoma-related early-stage HLH is difficult. The reported common clinical features of NK/T-LAHLH include: Fever,[12,33] splenomegaly,[12,15,33] lymphadenopathy,[12] younger age,[11,15] type B symptoms,[15] Ann Arbor stage III/IV,[15] international prognostic index (IPI) score ≥3,[15,34] bone marrow involvement.[11,15] Furthermore, the most common laboratory test features were hyperferriminemia,[12,33] cytopenia,[12,15,33] hypertriglyceridemia,[12,33] hypofibrinogenemia,[12,33] liver dysfunction,[12] elevated lactate dehydrogenase (LDH),[12,15] decreased serum albumin levels,[15] and the higher positive rate of EBV.[34] Multivariate analysis showed that the risk factors of NK/T-LAHLH were higher Eastern Cooperative Tumor Group (ECOG) score,[33] upper respiratory extrinsic NK/T-cell lymphoma (EUNKTL),[33] skin involvement,[33] bone marrow involvement,[12] hepatosplenomegaly,[12] and elevated LDH,[12,15] Ann Arbor stage III/IV,[15] younger age[15] and decreased serum albumin level.[15]

Treatment of NK/T-LAHLH

Currently, no unified or effective first-line treatment for NK/T-LAHLH exits.[13,15,35] The treatment regimens for NK/T-LAHLH mainly include the HLH-1994/HLH-2004 regimen, a chemotherapy regimen containing L-asparaginase or pegaspargase, and the DEP (liposomal doxorubicin, etoposide and methylprednisolone) regimen. The above regimens mainly focus on the treatment of HLH itself. There are also many studies reporting that patients directly receive chemotherapy regimens for lymphoma. In conclusion, in the current reports on NK/T-LAHLH, various treatment regimens have been applied, and the therapeutic responses have varied (Table 1). However, current studies on the treatment of NK/T-LAHLH are limited in number and generally small in sample size, making it difficult to draw definitive conclusions about the efficacy of specific therapeutic agents. Moreover, in the treatment of NK/T-LAHLH, the treatment of lymphoma itself is very important. After HLH is controlled, a transition to the treatment of lymphoma should be made as soon as possible in order to achieve long-term survival.

In the treatment of HLH, etoposide and dexamethasone-based HLH-1994 regimen and HLH-2004 regimen are still recommended as first-line therapy.[35,38] Therefore, for the treatment of NK/T-LAHLH, this type of regimen is relatively common and has achieved good therapeutic effects. He et al reported that 70 patients with NK/T-LAHLH were treated using the HLH-2004 regimen.[14] Although the complete response (CR) rate was only 4.3%, the total efficacy rate was 58.6%. Wei et al reported that patients with NK/T-LAHLH received etoposide in combination with dexamethasone-based combination chemotherapy.[13] In 21 patients newly diagnosed with lymphoma-based HLH, the overall response (OR) rate was 66.7%. In addition, Jin et al reported 36 cases of NK/T-LAHLH, where in addition to the HLH-1994 and HLH-2004 regimens, some patients still received lymphoma chemotherapy and glucocorticoid therapy regimens alone, with a total effective treatment rate of only 33.4%.[37]

In addition, some studies have reported that patients directly receive chemotherapy regimens for lymphoma. For instance, Liu et al reported 28 cases of NK/T-LAHLH.[33] After DICE (ifosfamide, etoposide, cisplatine, and dexamethasone) regimen with or without radiotherapy, asparaginase-based chemotherapy, and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen, the CR rate was 50%, OR rate was 71.4%, and a good response rate was

Table 1 Treatment Regimens and Responses for NK/T-LAHLH

Reference	Treatment Opportunity	N	Regimen	Time of Response	CR	PR	OR
Han et al 2014[34]	Induction therapy	15	Steroids, chemotherapy with or without pegaspargase	NA	9.1%	36.4%	45.5%
Jia et al 2016[11]	Induction therapy	23	Chemotherapy combined with L-asparaginase or pegaspargase, CHOP-like,vincristine and steroids	NA	NA	NA	4(17.4%)
Li et al 2017[36]	Induction therapy	7	MEDA	NA	4(57.1%)	2(28.5%)	6(85.4%)
Jin et al 2017[37]	Induction therapy	36	HLH-1994, HLH-2004, chemotherapy, glucocorticoids	NA	5.6%	27.8%	33.4%
Liu et al 2019[33]	Induction therapy	28	DICE with or without radiotherapy, asparaginase-based chemotherapy, CHOP	NA	14 (50%)	6 (21.4%)	20 (71.4%)
Wei et al 2020[13]	Induction therapy	21(ND-ENKTL)	Etoposide+dexamethasone-based chemotherapy	NA	38.1%	28.6%	66.7%
		16(R/R-ENKTL)	Etoposide+dexamethasone-based chemotherapy	NA	0	18.8%	18.8%
He et al 2022[14]	Induction therapy	70	HLH-2004	2 weeks	4.3%	54.3%	58.6%
He et al 2022[14]	Induction therapy	28	DEP	2 weeks	0	67.9%	67.9%
Meng et al 2022[15]	Induction therapy	14	L-DEP/DEP	2 weeks	0	11(78.6%)	11(78.6%)

Abbreviations: NK/T-LAHLH NK/T, cell lymphoma-associated hemophagocytic lymphohistiocytosis; CR, complete response; PR, partial response; OR, overall response; ND-ENKTL, Newly diagnosed extranodal NK/T-cell lymphoma; R/R-ENKTL, relapsed/refractory extranodal NK/T-cell lymphoma; NA, not available; CHOP, (cyclophosphamide, doxorubicin, vincristine, and prednisolone); MEDA, (methotrexate, etoposide, dexamethasone, and pegaspargase); DICE, (ifosfamide, etoposide, cisplatine, and dexamethasone); L-DEP, (pegaspargase, liposomal doxorubicin, etoposide and methylprednisolone).

https://doi.org/10.2147/BLCTT.S574445

obtained. However, Jia et al reported that 23 patients received chemotherapy, including CHOP-like regimens, and the total response rate post-treatment was only 17.4%.[11] The response rate varied among patients who primarily received a chemotherapy regimen for lymphoma.

The DEP regimen was initially reported as a salvage treatment for relapsed/refractory HLH in adults, and the total efficacy rate post-treatment was 76.2%.[39] Since then, the DEP regimen has been reported to treat various types of HLH, all of which have shown good therapeutic response.[40–43] Compared to the traditional HLH regimen, the DEP regimen included a new drug, liposomal doxorubicin, with a mechanism of action involving the primary targeting of activated monocytes and macrophages.[44,45] In a clinical study of lymphoma-associated HLH, the OR rates after 4 weeks of first-line treatment with the DEP and HLH-1994 regimens were 89.4% and 68.0%, respectively, suggesting that the DEP regimen was superior to the HLH-1994 regimen.[41] He et al reported that 28 patients with NK/T-LAHLH received the DEP regimen for 2 weeks and had a total effective rate of 67.9%, achieving a good therapeutic response.[14] In another clinical study on NK/T-LAHLH, some patients received DEP regimen-based pegaspargase, with a total effective rate of 78.6% following 2 weeks.[15] These studies suggest that the DEP regimen may be suitable for treating NK/T-LAHLH.

At present, studies have shown that pegaspargase targets tumour cells, causing them to fail to synthesise L-asparagine and die. It may also target EBV-infected T and NK cells, inhibiting the proliferation of EBV-infected cells, resulting in a decline of EBV-DNA.[46,47] Therefore, pegaspargase may be more suitable for patients with NK/T-LAHLH, as >90% of these patients are EBV-positive. Han et al added pegaspargase to a chemotherapy regimen for NK/T-LAHLH, achieving a total response rate of 45.5%.[34] In a clinical study by Li et al, seven patients with NK/T-LAHLH were treated with a MEDA (methotrexate, etoposide, dexamethasone, and pegaspargase) regimen containing pegaspargase, with an OR rate as high as 85.4%.[36] In addition, the total response rate of NK/T-LAHLH was 78.6% with the pegaspargase-containing an L-DEP/DEP regimen.[41] Thus, pegaspargase is an important therapeutic agent for patients with NK/T-LAHLH.

The JAK1/JAK2 inhibitor, ruxolitinib, treats HLH by blocking the JAK-STAT pathway and reducing the production of inflammatory factors.[48–53] Currently, ruxolitinib is used to treat NK/T-LAHLH. For instance, Zhou et al reported that ruxolitinib combined with DED (doxorubicin, etoposide, and dexamethasone) regimen was used to treat lymphoma-associated HLH.[54] Among them, 36 patients (23 with NK/T-LAHLH) treated with the R-DED regimen had total response rate of 83.3%, significantly higher than that of the HPH-1994 regimen (54.8%). However, patients with NK/T-LAHLH were excluded from this analysis. Zhao et al reported that a patient with NK/T-LAHLH achieved partial remission post-treatment with ruxolitinib and dexamethasone.[55] Therefore, ruxolitinib combination therapy may be a safe and effective treatment option for patients with NK/T-LAHLH.

Immune checkpoint inhibitors have been widely used to treat relapsed/refractory NKTL,[56–58] as programmed cell death protein 1 (PD-1) inhibitors have been reported to improve the overall survival of patients with NK/T-LAHLH. He et al reported on 98 NK/T-LAHLH cases,[14] after receiving the HLH-2004 and DEP regimens to treat HLH, the patients were coupled with anti-ENKTL chemotherapy with or without a PD-1 inhibitor. They found that patients treated with a PD-1 inhibitor achieved better survival. He et al also discovered that the EBV DNA of patients in the group receiving anti-ENKTL chemotherapy combined with a PD-1 inhibitor was significantly lower than before.[14] Moreover, Liu et al documented seven cases of relapsed/refractory EBV-associated HLH were treated with PD-1 inhibitors, of which six cases showed a treatment response and five cases achieved and maintained clinical complete remission,[59] with EBV-DNA being negative in four patients. Therefore, the use of PD-1 inhibitors in HLH induction therapy was attempted for EBV-positive NK/T-LAHLH. Xu et al reported that two patients with ENKTL-related HLH were treated with a PD-1 inhibitor combined with chidamide, and that HLH and ENKTL were alleviated post-treatment.[60] Two patients achieved durable survival without immune-related adverse events. Thus, PD-1 inhibitors can safely and effectively treat NK/T-LAHLH.

Hematopoietic stem cell transplantation (HSCT) is recommended for patients with primary and relapsed/refractory HLH. Currently, few studies exits on patients with NK/T-LAHLH receiving HSCT, of which, most are case reports and small-sample clinical studies. Inoue et al reported that a patient with NK/T-LAHLH did not respond to treatment with etoposide and glucocorticoid, and PR was obtained following treatment with SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) regimen combined with local radiotherapy. Additionally, CR was obtained after autologous HSCT (auto-HSCT), and a second auto-HSCT was performed post-chemotherapy,[61] and the CR continued following 2 years of follow-up. Liu et al reported a patient with NK/T-LAHLH who received allogeneic

HSCT (allo-HSCT) post-HLH treatment and remained alive at the last follow-up.[33] In addition, Han et al reported that four cases of lymphoma-associated HLH underwent auto-HSCT, of which one case was ENKTL, and achieved PR post-transplantation.[62] In another study involving 48 cases of NK/T-LAHLH, six patients survived to the last follow-up, of which two received auto-HSCT and two received allo-HSCT.[41] Recent studies have shown that HSCT improved the prognosis of patients with NK/T-LAHLH and prolonged their survival. Therefore, HSCT is recommended in patients with NK/T-LAHLH.

In conclusion, for the induction therapy of newly diagnosed NK/T-LAHLH patients, it is recommended to accept regimens containing chemotherapy drugs, such as the HHL-1994 regimen, HHL-2004 regimen, DEP regimen and MEDA regimen. Moreover, the combination of the above chemotherapy regimens with pegaspargase or ruxolitinib can achieve a better response. For relapsed/refractory NK/T-LAHLH, the combination of PD-1 inhibitors on the basis of the above chemotherapy regimens may achieve a good therapeutic response. And HSCT can improve the prognosis of NK/T-LAHLH and prolong the survival.

Prognostic Factors of NK/T-LAHLH

NK/T-LAHLH has a poor prognosis and short survival time. Most studies have found that the median survival time of such patients is <1 month, and occasional reports have indicated that the median survival time is >2 months.[11,33,34,41] Therefore, exploring the factors that can predict patient survival has always been an important focus of clinical research. Several studies identified various prognostic factors. For instance, Liu et al found that elevated serum LDH, hypofibrinogenaemia, and splenomegaly suggests poor survival in patients with NK/T-LAHLH.[33] Meanwhile, Jia et al found that patients with NK/T-LAHLH, an LDH level >1000 U/L, and disseminated intravascular coagulation had a shorter survival time.[11] In addition, Han et al found that poor survival in NK/T-LAHLH was associated with the following predictors: HLH onset at lymphoma diagnosis, high Ki-67 index, and poor treatment response.[34] Using multivariate Cox regression model analysis, Wei et al found that relapsed/refractory NKTL and non-nasal disease were independent risk factors for poor survival and prognosis in patients with NK/T-LAHLH.[11] He et al conducted multivariate analysis to determined that ECOG PS ≥2 was an independent prognostic risk factor for NK/T-LAHLH.[14] Therefore, PD-1 inhibitor and pegaspargase treatment were independent factors for prolonged survival. The above mentioned predictors are of great significance for predicting NK/T-LAHLH prognosis and guiding clinical treatment in advance.

Conclusions

NK/T-LAHLH is a rare clinical syndrome associated with poor treatment outcomes, high mortality rates, and an unclear pathogenesis. NKTL and HLH have many overlapping clinical features, such as fever, hemocytopenia, hepatosplenomegaly, liver function impairment, and elevated lactate dehydrogenase. Therefore, for NKTL patients with rapid disease progression and organ failure in the short term, HLH should be vigilant, and serum ferritin, soluble CD25 and NK cell activity should be paid attention to HLH related indicators to determine whether there is HLH. In addition, studies have found that chemotherapy regimens based on etoposide and dexamethasone, such as the HLH-1994 and HLH-2004 regimens, DEP regimen, and MEDA regimen, can enable NK/T-LAHLH patients to achieve good therapeutic responses. And HSCT can improve the long-term prognosis of patients. However, no recognised unified first-line treatment regimen exists for NK/T-LAHLH. Thus, an appropriate and effective treatment regimen needs to be further explored.

Data Sharing Statement

No datasets were generated or analysed during this study.

Funding

This work was supported by Natural Science Foundation of Shandong Province (ZR2025MS1378, ZR2024QH282) and Scientific Research Nurturing Fund of the First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital (QYPY2025NSFC0801).

Disclosure

There are no conflicts of interest.

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