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REVIEW

Lymphoma for the acute physician: diagnostic challenges and initial treatment decisions

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Abstract

Prompt diagnosis of lymphoma facilitates early treatment and improves outcomes for patients. For non-haemato-oncologists, it is important to have an understanding of how lymphoma can present and the initial work-up. This review is intended to provide clinicians with background to aid clinical decisional making at presentation and when managing treatment related complications. There will be particular emphasis on emergency presentations (tumour lysis syndrome, management of patients with a mediastinal mass, infections in lymphoma patients) and novel treatment options which have unique toxicities often requiring multi-specialty expertise.

Key words: Cellular therapy; Haematological emergencies; High grade lymphoma; Lymphoma

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Introduction

Lymphoma is the most common type of blood cancer (Zhang et al, 2023) and is a malignancy of the lymphatic system and related tissue. Commonly, lymphoma presents with lymphadenopathy detected clinically or radiologically. However, it can affect any organ system and may present with skin lesions, neurological symptoms (in central nervous system (CNS) lymphoma) or following investigations for abnormal haematological or biochemical blood tests. The treatment landscape for lymphoma has evolved in recent years, whereby traditional cytotoxic chemotherapy is now complemented by novel targeted therapies, some of which involve harnessing the host immune system against the tumour. As a result, outcomes for patients are improving significantly, but the unique toxicities of these treatments often require multi-specialty support. This review is designed for the acute physician to help facilitate the investigation and management of new presentations of lymphoma, as well as specific treatment complications which may be encountered in the general medical or critical care settings.

Lymphoma classification

As knowledge of the biological basis for lymphoma advances, the sub-classification of this heterogeneous disease becomes ever more complex. The updated WHO classification from 2022 lists 79 subtypes of mature B-cell neoplasms and 39 T- or Natural Killer (NK) cell lymphomas (Alaggio et al, 2022). Ultimately, the lineage of the neoplastic cell, together with the stage (number and distribution of nodal sites plus involvement of extranodal sites) and grade (a measure of tumour proliferation) determines treatment approach and prognosis.

Lymphoma can be subcategorised in a number of ways (see Figure 1), with the most important initial distinction being between Hodgkin (HL) and non-Hodgkin lymphoma (NHL). Classical HL (the most common HL subtype) is a distinct entity associated with the presence of Reed-Sternberg cells (derived from B-cells) in a biopsy specimen (Follows et al, 2014). NHL comprises all other lymphoma subtypes, the majority of which are B-cell in origin.

The next important sub-classification is between high grade and low grade lymphoma. High grade lymphomas are those where the neoplastic cells are rapidly proliferating and therefore often present with a short history of symptoms (weeks to months), often with

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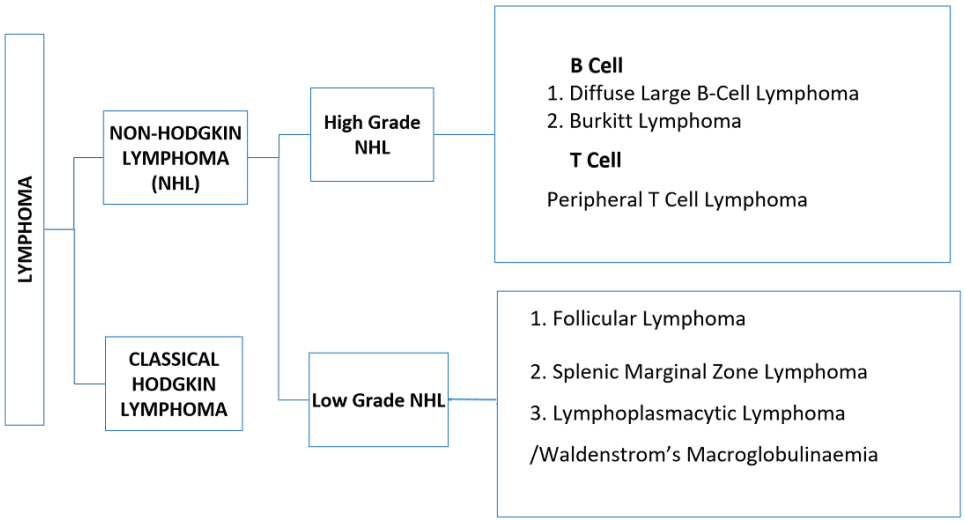

Figure 1. Simplified schema for lymphoma classification with examples of most frequently encountered subtypes. NHL, non-Hodgkin lymphoma.

large volume disease and sometimes critical organ compromise. Low grade lymphomas behave in a more indolent fashion, often being detected coincidentally and not necessarily requiring treatment. They do, however, require close follow-up as clinical progression to the point where treatment is required is inevitable for many, and they also have the ability to transform into high grade disease.

T-cell lymphoma is less common and can present with either localised skin involvement (cutaneous T-cell lymphomas) or with a combination of nodal and extra-nodal disease akin to a high grade B-cell lymphoma (peripheral T-cell lymphoma). These subtypes generally confer a poor prognosis.

Investigation of suspected lymphoma

The key step in lymphoma diagnosis is acquisition of a sufficient biopsy specimen of involved tissue. Complete staging requires imaging of the neck, chest, abdomen and pelvis. Computerised Tomography (CT) is often used as the initial imaging modality, however Positron Emission Tomography Computerised Tomography (PET-CT) is more sensitive and may 'upstage' some lymphomas by detecting disease not seen on CT (Ngeow et al, 2009). PET-CT can detect bone marrow involvement in Diffuse Large B-cell lymphoma (DLBCL) and Classical Hodgkin Lymphoma (cHL), however bone marrow examination is often still required for full staging in other lymphomas (e.g. follicular lymphoma) as PET-CT is less sensitive in these entities (Nakajima et al, 2020). Extensive lymphomatous bone marrow infiltration may be present even with a normal full blood count. Fine needle aspiration of nodal tissue for diagnosis should be avoided in preference for a core or excision biopsy. Occasionally, a diagnosis can be made from flow cytometry analysis of peripheral blood (where the lymphoma is 'exfoliating' from bone marrow), cerebrospinal fluid (CSF) in CNS lymphoma or pleural/pericardial effusions.

Definitive sub-typing is achieved using laboratory techniques including immunohistochemistry (IHC). IHC determines the lineage and maturity of neoplastic cells by detecting particular antigens present on the cell surface or cytoplasm. While for many years IHC was the only modality available to aid lymphoma sub-typing, more recently the diagnosis is often reached using a combination of IHC and specific genetic analyses (e.g. fluorescent *in situ* hybridisation, next generation sequencing).

Most patients require an echocardiogram to assess baseline cardiac function, as lymphoma regimens often include anthracycline chemotherapy which can cause acute and long-term cardiac toxicity (Volkova and Russell, 2011). Testing for HIV, Hepatitis B and C should be performed – some lymphomas arise in association with these blood-borne viruses, and detection of latent infection may necessitate additional prophylaxis during lymphoma

treatment. Measurement of lactate dehydrogenase (LDH) is useful, although elevated levels are not specific to lymphoma. Certain lymphomas are associated with a monoclonal paraprotein and this may be clinically relevant (e.g. very high IgM paraprotein in association with lymphoplasmacytic lymphoma can cause hyperviscosity syndrome). Clinicians should be mindful for any neurological symptoms which may suggest CNS involvement with lymphoma, with a low threshold for CNS imaging using contrast enhanced MRI as well as lumbar puncture/CSF examination. Certain high risk lymphomas (e.g. Burkitt lymphoma) require baseline lumbar puncture and CSF examination to exclude CNS disease even in the absence of neurological symptoms (often with intrathecal chemotherapy given concurrently).

General principles of lymphoma management

Active observation is often the initial management approach for low grade lymphoma, with regular review for the presence of systemic symptoms (significant weight loss, drenching sweats and/or itch) and clinical examination to determine progressive lymphadenopathy or organomegaly. Cytopenias due to progressive marrow disease may represent another indication for treatment. Early treatment of asymptomatic patients with low disease burden does not improve outcomes. Treatment when initiated in low grade disease is aimed at suppressing the disease for as long as possible but is rarely curative.

In contrast, treatment intent in high grade lymphoma is often curative. The most common high grade B-cell neoplasm is Diffuse Large B-cell lymphoma (DLBCL) which has a 60–70% 5 year survival rate with modern first line therapies (Crump et al, 2017). High grade disease can be suspected from rapidly rising LDH, systemic symptoms or rapidly enlarging nodal masses. PET-CT scanning can sometimes be useful as particular patterns of avidity radiologically may suggest high grade disease.

The most common treatment in high grade B-cell lymphoma is the combination of the anti-CD20 antibody Rituximab with ‘CHOP’ (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy.

Although similar chemoimmunotherapy combinations are often used when treatment is required in low grade lymphomas, in recent years there has been a move towards ‘chemotherapy free’ treatment for some subtypes. The most widely used currently are bruton’s tyrosine kinase (BTK) inhibitors (e.g. Ibrutinib). These drugs inhibit signalling pathways essential for B-cell development and signalling. Increased bleeding risks and cardiac toxicity are associated with Ibrutinib, however subsequent ‘second generation BTK inhibitors’ (e.g. Zanubrutinib and Acalabrutinib) appear to be as effective with less toxicity (see Alu et al, 2022).

Outcomes for young adults with cHL using intensive chemotherapy are excellent with 5 year overall survival in excess of 90% (Munir, et al. 2023). There is also a second peak in incidence of cHL in older adults where outcomes are less favourable due to inability to tolerate such intensive regimens. For this reason there is a move towards using novel agents (e.g. the anti CD30 antibody-drug conjugate Brentuximab vedotin) in this cohort to reduce toxicity and improve outcomes.

Autologous stem cell transplantation has a therapeutic role as first line consolidation in certain lymphomas (e.g. primary CNS lymphoma) or in the relapsed/refractory setting. Cellular therapies are another alternative option in relapsed/refractory disease, the most established being chimeric antigen receptor (CAR) T-cell therapy (discussed below).

Management of a patient presenting with a mediastinal mass

Any patient presenting with lymphadenopathy concerning for lymphoma should have a chest X-ray performed to exclude a significant mediastinal mass (Figure 2). Overall, lymphomas are responsible for 15% of all primary mediastinal masses, however it is the most common cause in young adults, typically due to either cHL or primary mediastinal large B-cell lymphoma. Other causes include germ cell tumours and primary lung cancer.

Age, smoking history and chronicity of symptoms are important components of the clinical history and a testicular examination should be performed in men. Tumour markers

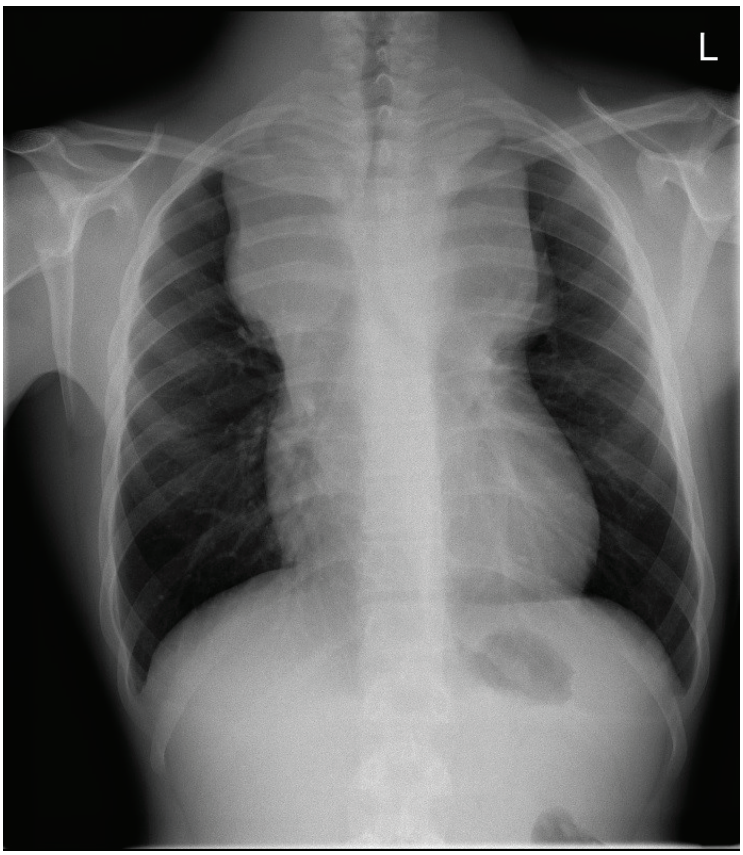

Figure 2. Young adult presenting with a large mediastinal mass on chest X-ray (subsequent biopsy diagnostic of Classical Hodgkin Lymphoma). L, left.

(LDH, beta human chorionic gonadotropin and alpha feta protein) are indicated as these may indicate a diagnosis of germ cell malignancy.

Lymphomas are often extremely sensitive to steroids, indeed many common lymphoma chemotherapy regimens incorporate short pulses of steroids. As an initial treatment they can cause rapid tumour shrinkage, particularly in high grade lymphomas, and therefore relieve critical organ compression. Unfortunately, if given before a diagnostic biopsy specimen has been taken, they can significantly alter histological tissue appearances and impair the diagnostic yield from the specimen. Therefore, where possible it is advisable to withhold steroids until a tissue biopsy has been obtained and confirmation of viable lymphoma tissue received.

Patients who present with a mediastinal mass causing hypoxia, respiratory distress, stridor or those who are unable to lie flat should be considered for urgent treatment, even before a tissue biopsy. Local protocols should be in place regarding emergency steroid dosing and/or chemotherapy. Such patients should be managed in a critical care environment. Tumour lysis risk (see later section) should be identified and managed. Our approach to this clinical scenario is to use high dose methylprednisolone and if progressive symptoms despite this to use a chemotherapy agent with broad activity against both haematological and solid organ malignancies. Respiratory symptoms may relate not only to airway compression but also to superior vena cava obstruction, pericardial invasion or malignant pleural effusion. Bone marrow biopsy may be an alternate route to a tissue diagnosis where lymph node biopsy is not initially feasible if peripheral blood parameters are suggestive of marrow involvement.

Similar considerations should be applied to patients presenting with malignant spinal cord compression where lymphoma is in the differential diagnosis. Here, biopsy may be more technically difficult and steroids should be given at the earliest possible juncture to prevent neurological compromise. This is usually sufficient to relieve critical cord compression while biopsy is explored, with chemotherapy rarely required before diagnosis confirmation.

Treatment complications: tumour lysis syndrome

This is an acute metabolic disturbance due to the release of tumour cell contents into the circulation. It can occur spontaneously or, more commonly, on initiation of systemic anti-cancer therapy (including corticosteroids). High grade lymphomas are associated with high risk of tumour lysis syndrome (TLS) – this increased risk may be indicated by significantly elevated LDH levels. Additional risk factors include the presence of high tumour bulk or renal impairment.

Lysis of cells causes release of phosphate, potassium, inflammatory cytokines and DNA. The characteristic biochemical picture is acute elevation of phosphate, potassium and creatinine with a drop in adjusted calcium (high phosphate causes chelation of calcium). Laboratory TLS refers to the presence of these characteristic blood parameters, while clinical TLS refers to the biochemical abnormalities in association with clinical manifestations of either acute kidney injury, seizures, cardiac dysrhythmia, or death (see Table 1) (Cairo and Bishop, 2004).

Management of TLS involves close monitoring of fluid balance, electrolytes and renal function. Allopurinol can be given as prophylaxis of TLS as it inhibits xanthine oxidase formation and reduces crystal deposition by reducing formation of uric acid. Rasburicase works at a later stage of this biochemical pathway by catalysing uric acid to the inactive allantoin. Rasburicase is more potent than allopurinol and is used as prophylaxis in patients who are at higher risk of TLS. If established biochemical or clinical TLS occurs then immediate initiation of 'treatment dose' Rasburicase (0.2 mg/kilogram) is used. TLS carries high morbidity, therefore early liaison with renal and critical care teams is needed. Cardiac monitoring and medical management of hyperkalaemia are useful initial steps, however early consideration of renal replacement therapy is recommended in established TLS not responding to the above measures.

Treatment complications: infection in patients with lymphoma

Patients with lymphoma are at an increased risk of a range of viral, bacterial and fungal infections, related to immune dysregulation due to the disease process and also treatment related mechanisms (Lutz et al, 2023). Certain infections (e.g. Hepatitis B) may reactivate in an immunocompromised state during treatment with drugs like Rituximab. Oral antivirals and regular monitoring of liver function and hepatitis B serology during/post treatment (Villadolid et al, 2010) are occasionally required.

Infection risk can be increased by hypogammaglobinaemia and failure to produce adequate response to vaccination. Many common lymphoma regimens are associated with a predictable, but short-lived, period of neutropenia and therefore local protocols should be in place for the management of neutropenic sepsis. Certain chemotherapy regimens

Table 1. Tumour lysis syndrome: diagnostic classification (Cairo and Bishop, 2004)

Laboratory TLS: Two or more of the laboratory abnormalities below within 3 days before or 7 days after initiation of treatment.	Clinical TLS: Criteria for laboratory TLS and any of the signs of end-organ damage below when they are not attributable to an alternate aetiology.
Phosphorus ≥ 4.5 mg/dL or ≥ 25% increase from baseline	Cardiac arrhythmia/sudden death
Potassium ≥ 6 mEq/L or ≥ 25% increase from baseline	Creatinine ≥ 1.5× upper limit normal
Uric acid ≥ 8 mg/dL or ≥ 25% increase from baseline	Seizure
Calcium ≤ 7 mg/dL or ≥ 25% decrease from baseline	

Abbreviations: TLS, tumour lysis syndrome.

contain prophylactic granulocyte colony stimulating factor (GCSF) to reduce duration of neutropenia. Patients may have indwelling vascular access lines which should always be considered as a potential source of sepsis. Clinical consideration should be given to atypical pathogens (e.g. Pneumocystis jirovecii pneumonia (Zhang et al, 2022) in febrile patients with respiratory symptoms not improving despite broad spectrum antibiotics. John Cunningham (JC) virus should be considered in patients with unexplained confusion or progressive neurological symptoms (Goldman et al, 2023) who have had previous lymphoma treatment.

Treatment complications: immunotherapy toxicities

Chimeric antigen receptor T-cells are manufactured on an individual patient basis following autologous apheresis collection of T-cells which are modified *in vitro* to express a novel receptor which can bind to antigen on the tumour, causing cell death. This manufacturing process often takes 4–6 weeks in total, with the CAR T-cells then reinfused to the patient immediately after 'conditioning' chemotherapy. There are several commercially available CAR T-cell products which may confer durable remissions for some patients with relapsed/refractory lymphoma (traditionally a situation associated with very poor prognosis).

Bispecific antibodies (BSAbs) also harness the endogenous T-cell response but do so by concurrently binding to tumour antigen and host T-cells *in vivo*, resulting in T-cell mediated tumour cell death. Importantly, these drugs do not require the same individual manufacturing process used in CAR T-cell therapy and therefore can be administered 'off the shelf'. A range of BSAbs (e.g. glofitimab and epcoritamab) have shown therapeutic benefit in the relapsed setting for B-cell lymphoma (Falchi et al, 2023)

The resultant hyper-stimulation of the host immune system from these therapies results in a particular toxicity known as cytokine release syndrome (CRS) which is characterised by fever, hypotension and end organ dysfunction. CRS occurs with both CAR T-cell and BSAbs, however severe CRS is more common with CAR T-cells (around 8% from UK data) (Gurumurthi et al, 2023). Table 2 describes the grading system used for CRS (irrespective of cause) and provides a useful guide for principles of management (Lee et al, 2019). Individual, centre-specific protocols should be in place for management of CRS. Input from critical care teams is crucial for these patients, with transfer to level 2 or level 3 units sometimes required to facilitate delivery of vasopressors and/or supplemental oxygen or other organ support.

Cytokine release syndrome treatments are focussed on reducing inflammation and cytokine release. High dose steroids, tocilizumab (interleukin-6 antagonist) and anakinra (interleukin-1 receptor antagonist) can be used to manage toxicities (Jain et al, 2023). In early CAR T-cell trials, there was concern that these immunosuppressive drugs may impact efficacy of cellular therapies, however this has not been borne out by subsequent data and

Table 2. Cytokine release syndrome grading system (Lee et al, 2019)

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥38°C	Temp ≥38°C	Temp ≥38°C	Temp ≥38°C
With either:				
Hypotension	None	Responsive to intravenous fluids	Requiring a vasopressor	Requiring multiple vasopressors
And/Or				
Hypoxia	None	Supplementary oxygen therapy (≤6 L/min)	Supplementary oxygen therapy (>6 L/min)	Requiring NIV, high flow nasal oxygen or intubation and mechanical ventilation

CRS, cytokine release syndrome; NIV, non-invasive ventilation.

there is now a move to use steroids and cytokine blocking drugs earlier with minor toxicities or even prophylactically pre-infusion to reduce morbidity.

Neurotoxicity (known as Immune cell-associated neurotoxicity syndrome – ICANS) is another unique toxicity seen with certain immunotherapies, most frequently with CAR T-cell therapy. It tends to occur acutely (within days of CAR T-cell administration) but in a small proportion of patients can occur more than 3 weeks after infusion. Clinical presentation is varied but an early feature is deterioration in co-ordination (often picked up clinically by deterioration in handwriting), with some cases progressing to altered conscious level and seizure activity. ICANS is thought to be due to breakdown in the blood brain barrier rather than directly mediated by CAR T-cell themselves (Brudno and Kochenderfer, 2016). ICANS is rare with BSAb therapy (Gurumurthi et al, 2023). The mainstay of ICANS management is supportive with critical care and neurology team involvement, with use of anti-cytokine and corticosteroid therapy as described for CRS. Fortunately, the majority of patients recover completely from this toxicity with no or minimal neurological sequelae.

Treatment complications: cardiac toxicity

Anthracycline chemotherapy forms the backbone of many lymphoma treatment regimens. Anthracyclines may cause acute cardiac toxicity but more commonly it occurs as a late effect presenting as a dilated/hypokinetic cardiomyopathy (Cardinale et al, 2020). The diagnosis can be missed as patients may be young and lack traditional cardiac risk factors. Concurrent hypertension, diabetes and dyslipidaemia should be identified and managed. Unfortunately, there is often a poor response to traditional heart failure treatment. Biomarkers such as troponin and brain natriuretic peptide may provide a useful pointer to the diagnosis.

BTK inhibitors (e.g. Ibrutinib) have been associated with cardiac toxicity. Rates of atrial fibrillation range from 5–16% (Pineda-Gayoso et al, 2020) and ventricular arrhythmias have also been described (Guha et al, 2018). Where atrial fibrillation is persistent and anticoagulation is potentially indicated, careful consideration of the risks and benefits is required given the increased bleeding risk associated with BTK inhibitors due to platelet function alterations. Direct oral anticoagulant drugs can be used in this setting but vitamin K-antagonists should be avoided. Although rates of arrhythmia are lower with ‘second generation’ BTKi agents, all drugs in this class carry risk of hypertension which should be monitored closely and managed accordingly (see Chen et al, 2022)

Conclusion

The term ‘lymphoma’ comprises a heterogeneous group of haematological cancers, some of which behave very aggressively but are treated with curative intent in the majority of patients. Patients often present to acute specialties and a multi-disciplinary approach is required to ensure timely confirmation of diagnosis and initiation of treatment. Early liaison with the haemato-oncology team at presentation is crucial, who will help guide initial investigations before taking over management and initiating therapy in a dedicated oncology unit. The therapeutic landscape for patients with lymphoma continues to evolve, improving outcomes but also introducing novel toxicities which may require input from multiple specialties. Therefore, it is important for all acute physicians to have an understanding of the potential complications which may arise and require their input in a general medical or critical care setting.

Key points

- Diagnostic classification and investigation of suspected lymphoma.
- Current management of low grade and high grade lymphoma.
- Efficacy and toxicity of cellular therapies.
- Long term treatment related morbidity from lymphoma chemoimmunotherapy.

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Availability of data and materials

All the data of this study are included in this article.

Author contributions

Manuscript was jointly written and designed by RDH and MRW. Both authors contributed to important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest.

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