

Gastric Diffuse Large B-Cell Lymphoma: Clinicopathological Characteristics, Prognostic Factors, and Treatment Outcomes — A South Asian Tertiary Care Case Series.

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Abstract

Background: Primary gastric diffuse large B-cell lymphoma (DLBCL) accounts for 5-10% of gastric malignancies and represents approximately 3-6% of primary extranodal non-Hodgkin lymphomas. Limited data exist regarding clinicopathological features and outcomes in South Asian populations. Objective: Comprehensive characterization of clinicopathological features, prognostic factors, and treatment outcomes in a consecutive case series of gastric DLBCL from a South Asian tertiary care center. **Methods:** Retrospective analysis of 17 consecutive patients with histologically confirmed gastric DLBCL (January 2023-December 2025). Comprehensive data collection included demographics, comorbidities, clinical presentation, laboratory parameters, histopathology, immunohistochemistry, imaging findings, treatment protocols, and clinical outcomes. **Results:** Median age 48.7±12.4 years (70.6% <60 years); male predominance 55.6%. Profound hematologic abnormalities: anemia 94.1% (mean Hb 9.78 g/dL), elevated LDH 70.6%, hypoalbuminemia 88.2% (mean 3.13 g/dL). Remarkably high extra-nodal involvement: CNS 82.4%, bone marrow 82.4%. Double expressors (MYC+/BCL2+) in 17.6% with high proliferation (mean Ki67 69.4%). Advanced-stage disease: 58.8% Stage IV. Treatment response (n=8): 87.5% overall response rate (50% complete response, 37.5% partial response). Low relapse rate 5.9% during follow-up. **Conclusions:** Gastric DLBCL in this cohort presented with aggressive disease phenotype, extensive extra-nodal dissemination, and advanced-stage disease at presentation. The exceptionally high frequencies of CNS and bone marrow involvement warrant prospective validation. These findings underscore the importance of comprehensive staging and intensive treatment approaches in gastric DLBCL management.

Keywords: Gastric lymphoma; diffuse large B-cell lymphoma; DLBCL; immunohistochemistry; double expressors; CNS involvement; bone marrow involvement; prognostic factors; South Asian populations.



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INTRODUCTION

Primary gastric lymphoma accounts for 3-6% of all gastric malignancies and represents the most common site of primary extranodal non-Hodgkin lymphoma (NHL), with diffuse large B-cell lymphoma (DLBCL) being the predominant histological subtype accounting for 50-60% of primary gastric lymphomas. The stomach's rich mucosa-associated lymphoid tissue (MALT) creates a unique microenvironment predisposing to lymphoid proliferation, particularly in the setting of chronic inflammatory states such as *Helicobacter pylori* infection, autoimmune gastritis, and prior malignancy.¹⁻³ Epidemiological patterns demonstrate important geographic variations in the presentation and clinical course of gastric DLBCL. Western series consistently report peak incidence in the 7th-8th decade of life with slight male predominance. Emerging evidence from Asia-Pacific regions, however, suggests a younger age-at-diagnosis and potentially more aggressive disease phenotypes, indicating possible differences in etiopathogenesis, immune responses, or diagnostic factors in these populations.⁴⁻⁶

Contemporary WHO/International Agency for Research on Cancer (IARC) 2022 classification recognizes DLBCL as a heterogeneous collection of entities with distinct genetic, molecular, and clinical characteristics. Cell-of-origin (COO)

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classification, distinguishing germinal center B-cell (GCB) from activated B-cell (ABC/non-GCB) subtypes, carries important prognostic implications. GCB-type DLBCL typically demonstrates superior treatment responses and longer overall survival compared to ABC-type disease.⁷

Double-expressor DLBCL, defined by concurrent MYC and BCL2 protein overexpression in $\geq 40\%$ of tumor cells, represents an exceptionally aggressive subset with significantly inferior prognosis. These cases frequently harbor complex karyotypes, marked genomic instability, and high KI67 proliferation index ($>80\%$), stratifying patients into high-risk categories requiring intensified treatment approaches.^{8–10}

Central nervous system (CNS) involvement occurs in approximately 5–10% of DLBCL patients and carries catastrophic prognosis with median overall survival less than 6 months following CNS relapse. Similarly, bone marrow involvement portends poor prognosis and represents evidence of advanced systemic disease. Despite the clinical significance of gastric DLBCL, prospective management data remain limited, particularly in South Asian populations.^{11–12}

This comprehensive case series characterizes the clinicopathological features, prognostic factors, and treatment outcomes of gastric DLBCL in patients presenting to a South Asian tertiary care center, aiming to contribute to understanding of this disease in underrepresented populations.

MATERIALS AND METHODS

Study Design and Patient Selection

This retrospective case series included 17 consecutive patients with histologically and immunohistochemically confirmed gastric DLBCL presenting to the Department of Medical Oncology at Vydehi Institute of Medical Sciences and Research Centre, Bengaluru, between January 2023 and December 2025. Inclusion criteria encompassed: (1) histopathologically confirmed gastric DLBCL according to WHO/IARC 2022 classification; (2) age ≥ 18 years; (3) complete clinicopathological diagnostic data available; (4) baseline staging imaging performed prior to treatment initiation. Exclusion criteria included: (1) secondary gastric involvement from systemic lymphoma; (2) histological transformation from low-grade lymphoma; (3) concurrent primary malignancy; (4) incomplete diagnostic or outcome documentation. The study was approved by the Institutional Review Board with waiver of informed consent for retrospective analysis of existing clinical records.

Data Collection and Clinical Assessment

Comprehensive baseline data collection included: demographics (age, sex, contact history with infectious agents), relevant clinical history (prior malignancy, immunosuppression, organ transplantation), comorbidities (HIV status with CD4 count, diabetes mellitus, hypertension, chronic hepatitis), concurrent medications, smoking and alcohol use history, and detailed symptom assessment including B symptoms (fever $>38.5^{\circ}\text{C}$ for ≥ 3 consecutive days, drenching night sweats, unintentional weight loss $>10\%$ body weight over 6 months). Performance status was assessed using Eastern Cooperative Oncology Group (ECOG) criteria on a 0–4 scale.

Laboratory and Imaging Assessment

Comprehensive laboratory evaluation included: complete blood count with differential, comprehensive metabolic panel, coagulation profile, serum lactate dehydrogenase (LDH), viral serologies (HIV with CD4/CD8 counts, hepatitis B surface antigen, anti-hepatitis C antibody), and cardiac assessment (ejection fraction by echocardiography). Staging imaging workup included: upper gastrointestinal endoscopy with direct visualization and targeted biopsies, endoscopic ultrasound (EUS) for local staging, contrast-enhanced computed tomography (CT) of chest, abdomen, and pelvis, positron emission tomography with ^{18}F -fluorodeoxyglucose (PET-CT), brain magnetic resonance imaging (MRI) for high-risk patients, bone marrow trephine biopsy for hematologic assessment, and lumbar puncture with cerebrospinal fluid (CSF) analysis for CNS assessment.

Histopathological and Immunohistochemical Analysis

Gastric tissue biopsies were reviewed by experienced hematopathologists for histological diagnosis according to WHO/IARC 2022 classification criteria. Comprehensive immunohistochemical (IHC) panels included: B-cell markers (CD20), T-cell markers (CD3, CD4, CD8), germinal center markers (CD10, BCL6, MUM1), proliferation index (KI67), and anti-apoptotic markers (BCL2). Cell-of-origin (COO) classification was determined using the Choi algorithm based on IHC expression patterns. Double expressors were defined as concurrent MYC and BCL2 protein overexpression in $\geq 40\%$ of neoplastic cells.

Disease Staging and Risk Stratification

Disease staging was determined using the Ann Arbor staging system (stages I–IV) with modifications for gastric involvement and the modified Lugano staging system specific for gastric lymphomas. Prognostic factors assessed included:

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presence of B symptoms, bulky disease (>5 cm), CNS involvement, bone marrow involvement, number of extra-nodal sites involved, COO classification (GCB vs. ABC), double-expressor status, and Ki67 proliferation index.

Treatment and Response Assessment

First-line treatment regimens employed were individually documented from clinical records. Standard treatment regimen consisted of R-CHOP (rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² capped at 2 mg total dose, prednisone 100 mg orally daily × 5 days) administered every 21 days. Treatment response was assessed using Lugano 2014 criteria incorporating contrast-enhanced CT and PET-CT findings. Response categories included: Complete Response (CR) - complete resolution of disease, Partial Response (PR) - ≥50% reduction in tumor burden, Stable Disease (SD) - <50% reduction without progression, and Progressive Disease (PD) - >25% increase in tumor burden or new lesions.

Statistical Analysis

Descriptive statistics were used to characterize the cohort. Continuous variables were expressed as mean ± standard deviation (SD) with range; categorical variables as frequencies and percentages. Statistical significance was set at P<0.05. This descriptive case series was designed to characterize clinical features, pathological findings, and treatment outcomes rather than to perform hypothesis testing or comparative analysis.

RESULTS

Demographics and Clinical Characteristics

Seventeen consecutive patients with gastric DLBCL were analyzed during the study period. Median age at presentation was 48.7 ± 12.4 years (range 33-78 years). Age distribution was notable for predominance of younger patients: 70.6% (n=12) were <60 years old, compared to typical Western cohorts which report a peak in the 7th-8th decade. This younger age-at-diagnosis suggests possible population differences in disease biology or healthcare access patterns. Male-to-female sex ratio was 1.25:1 (males n=5, 55.6%; females n=4, 44.4%). Comorbidities were present in 64.7% of patients (n=11): HIV co-infection in 11.8% (n=2, both with CD4 count >200 cells/μL on antiretroviral therapy); diabetes mellitus in 11.8% (n=2); hypertension in 17.6% (n=3). Performance status at presentation was relatively preserved: ECOG 0-1 in 88.2% of patients (n=15). Presence of B symptoms was documented in 29.4% of patients (n=5), indicating more advanced and symptomatic disease in this subset.

Table 1. Demographic and Clinical Characteristics (n=17)

Variable	n (%)	Mean±SD
Total patients	17 (100%)	—
Age (years)	—	48.7±12.4
Age <60 years	12 (70.6%)	—
Male	5 (55.6%)	—
ECOG 0-1	15 (88.2%)	—
B symptoms	5 (29.4%)	—

Laboratory Findings

Comprehensive laboratory analysis revealed significant hematologic abnormalities at presentation, with anemia being nearly universal. Hemoglobin <12 g/dL was documented in 94.1% of patients (n=16), with mean hemoglobin 9.78 ± 1.23 g/dL (range 7.8-12.1 g/dL). This extraordinarily high prevalence of anemia reflects multiple contributory mechanisms including chronic blood loss from gastric tumor erosion and ulceration, bone marrow infiltration by lymphoma (documented in 82.4% of patients), systemic inflammation from active malignancy, and nutritional deficiencies.

Metabolic parameters revealed several abnormalities indicating high disease burden and systemic derangement. Elevated lactate dehydrogenase (LDH) was detected in 70.6% of patients (n=12) with mean LDH 328 ± 112 U/L (range 156-580 U/L), indicating high disease burden and accelerated cellular turnover. Serum hypoalbuminemia (<3.5 g/dL) was documented in 88.2% of patients (n=15) with mean albumin 3.13 ± 0.27 g/dL (range 2.6-3.8 g/dL), reflecting malnutrition, chronic disease state, and impaired hepatic synthetic function. Serum creatinine showed mean 0.75 ± 0.30 mg/dL with adequate renal function in most patients.

Table 2. Laboratory Parameters at Baseline (n=17)

Parameter	Mean±SD	Range	Abnormal %
Hemoglobin (g/dL)	9.78±1.23	7.8-12.1	94.1%
LDH (U/L)	328±112	156-580	70.6%
Albumin (g/dL)	3.13±0.27	2.6-3.8	88.2%

Histopathology and Immunohistochemistry

All 17 cases (100%) were confirmed as gastric DLBCL by histopathology and comprehensive immunophenotyping according to WHO/IARC 2022 classification criteria. Histological sections demonstrated characteristic DLBCL features including: diffuse infiltration by large B lymphocytes with vesicular nuclei, prominent nucleoli, abundant cytoplasm, elevated mitotic index, and frequent apoptotic figures, consistent with high-grade malignancy.

Immunohistochemical analysis revealed: CD20 expression was universally positive (100%, n=17). Ki67 proliferation index demonstrated mean $69.4 \pm 18.2\%$ (range 45-92%), with 70.6% of cases (n=12) showing Ki67 >60%. Notably, 29.4% (n=5) demonstrated ultra-high Ki67 >80%, representing exceptionally aggressive tumor biology. BCL2 positivity was observed in 23.5% (n=4) with mean expression $45 \pm 12\%$. BCL6 expression was noted in 35.3% (n=6) with mean expression $50 \pm 18\%$. MYC positivity was identified in 5.9% (n=1).

Critically, double expressors (concurrent MYC+ and BCL2+ $\geq 40\%$) were identified in 17.6% (n=3 cases), representing an exceptionally high-risk disease subset. This prevalence of double expressors (17.6%) exceeds typical unselected DLBCL cohorts (10-15%), suggesting more aggressive disease biology in this population. Cell-of-origin (COO) classification using Choi algorithm could be determined in 14 patients (82.4%): GCB-type identified in 52.9% (n=9), non-GCB/ABC-type in 47.1% (n=8). This approximately balanced distribution suggests molecular heterogeneity with both favorable (GCB) and less-favorable (ABC) prognostic phenotypes represented.

Table 3. Immunohistochemical Profile of Gastric DLBCL Cases (n=17)

IHC Marker	Positive n (%)	Mean Expression	Range (%)
CD20	17 (100%)	—	95-100
Ki67 (>60%)	12 (70.6%)	$69.4 \pm 18.2\%$	45-92
BCL2	4 (23.5%)	$45 \pm 12\%$	40-60
Double Expressor	3 (17.6%)	—	—

Disease Staging and Prognostic Factors

Comprehensive staging revealed predominantly advanced-stage disease at presentation according to Ann Arbor classification: Stage I in 23.5% (n=4); Stage II in 11.8% (n=2); Stage III in 5.9% (n=1); Stage IV (disseminated disease) in 58.8% (n=10). The predominance of Stage IV disease (58.8%) reflects systemic dissemination characteristic of high-grade aggressive lymphomas.

Most striking was the extraordinarily high frequency of extra-nodal involvement: CNS involvement in 82.4% (n=14); bone marrow infiltration in 82.4% (n=14). These frequencies substantially exceed typical gastric DLBCL cohorts reported in international literature, where CNS involvement ranges 0-15% and bone marrow involvement 5-25%. The disproportionate extra-nodal disease burden warrants critical interpretation and prospective validation. Multiple explanations may account for these findings: (1) this may represent a genuinely more aggressive disease phenotype in this geographic/ethnic population; (2) disease recognition occurred at a more advanced stage due to delayed presentation or diagnostic barriers; (3) the high prevalence may reflect the inclusion of patients with occult CNS or bone marrow disease identified through more intensive staging algorithms than commonly employed in practice; or (4) there may be misclassification of tissue involvement.

Additional prognostic factors included: bulky disease (>5 cm) identified in 11.8% (n=2); presence of B symptoms in 29.4% (n=5); extra-nodal sites >1 in 5.9% (n=1).

Table 4. Disease Stage and Prognostic Factors (n=17)

Prognostic Factor	Number (%)
Stage I	4 (23.5%)
Stage II	2 (11.8%)
Stage III	1 (5.9%)
Stage IV	10 (58.8%)
CNS Involvement	14 (82.4%)
Bone Marrow Involvement	14 (82.4%)
Double Expressor Status	3 (17.6%)

Treatment and Clinical Outcomes

Treatment documentation and complete follow-up data were available for 47.1% of patients (n=8); 52.9% had incomplete treatment protocol documentation. Among patients with documented treatment (n=8): All 8 patients received R-CHOP

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chemotherapy administered every 21 days. Treatment duration varied: 6 cycles in 2 patients, 8 cycles in 6 patients. Central nervous system prophylaxis with intrathecal methotrexate (12.5 mg) was administered in 37.5% (n=3) during treatment cycles. Notably, 62.5% (n=5) of treated patients did not receive documented CNS prophylaxis despite the extremely high CNS involvement rate in this cohort.

Response assessment among treatment-completed patients (n=8): Complete Response (CR) was achieved in 50% (n=4); Partial Response (PR) in 37.5% (n=3); Progressive Disease (PD) in 12.5% (n=1). Overall Response Rate (ORR = CR + PR) was 87.5%—a favorable rate and consistent with published R-CHOP efficacy data in DLBCL. Median follow-up duration was 18 months (range 3-42 months). During the follow-up period: disease relapse occurred in 1 patient (5.9%), who was treated with salvage chemotherapy. Documented treatment toxicities were limited but included: Grade 2 infection in 25% (n=2); significant anemia requiring transfusion support in 12.5% (n=1).

Table 5. Treatment Outcomes and Clinical Response (n=8 with documented treatment)

Treatment Response (n=8)	Number (%)
Complete Response (CR)	4 (50%)
Partial Response (PR)	3 (37.5%)
Progressive Disease (PD)	1 (12.5%)
Overall Response Rate (ORR)	7 (87.5%)
Relapse During Follow-up	1 (5.9%)

DISCUSSION

Clinical Presentation and Disease Phenotype

This case series of 17 patients with gastric DLBCL demonstrates several important clinical and pathological features. The median age of 48.7 years is consistent with published literature showing peak incidence in the 5th-7th decade; however, our cohort demonstrates a younger predominance (70.6% <60 years) compared to typical Western cohorts.¹³⁻¹⁴ The slight male predominance observed in this series (M:F ratio 1.25:1) aligns with global epidemiological trends.

A striking and concerning finding in this cohort was the extraordinarily high frequency of CNS involvement (82.4%) and bone marrow involvement (82.4%) at presentation. These frequencies far exceed previously reported rates in primary gastric DLBCL from the literature, which typically range from 0-15% for CNS involvement depending on risk stratification and imaging modality used.¹⁵⁻¹⁷ This disproportionate prevalence of extra-nodal involvement suggests several important possibilities: (1) this may represent a genuinely more aggressive disease phenotype in this geographic/ethnic population; (2) disease recognition occurred at a more advanced stage due to delayed presentation or diagnostic barriers; (3) the high prevalence may reflect the inclusion of patients with occult CNS or bone marrow disease identified through more intensive staging algorithms than commonly employed in practice; or (4) there may be misclassification of tissue involvement.

Hematologic and Metabolic Abnormalities

Anemia at presentation (94.1%) is a significant and concerning finding with multiple contributory mechanisms. Chronic blood loss from the gastric lesion through ulceration and erosion, bone marrow infiltration by lymphoma (documented in 82.4% of this cohort), and systemic inflammation secondary to active malignancy all contribute to severe anemia. The profound hypoalbuminemia (88.2%, mean 3.13 g/dL) reflects the combination of malnutrition, chronic disease state, and impaired hepatic synthetic function in these patients. Elevated LDH (70.6% of cases) indicates high disease burden and accelerated cellular turnover. These laboratory abnormalities collectively indicate advanced systemic disease with significant nutritional and metabolic derangement at presentation.¹⁸

Immunohistochemical Profile and Double-Expressor Disease

The high prevalence of double expressors (17.6%) in this series is noteworthy and biologically significant, exceeding the typical prevalence observed in unselected DLBCL cohorts (10-15%).¹⁹⁻²⁰ Double-expressor DLBCL (MYC+ and BCL2+ co-expression) has been recognized as a distinct high-risk category with significantly inferior prognosis compared to DLBCL with single-gene aberrations. The mean KI67 of 69.4% and the notable proportion of cases with ultra-high KI67 >80% (29.4%) further indicate exceptionally aggressive tumor biology. These high-risk immunophenotypic features likely contribute substantially to the advanced stage and extensive extra-nodal involvement observed in this cohort.

Treatment Response and Outcomes

Among patients who completed treatment (n=8, 47.1% of cohort), the 87.5% overall response rate (50% CR, 37.5% PR) is favorable and consistent with published R-CHOP efficacy data for DLBCL.²¹⁻²² However, the low numbers completing treatment and incomplete documentation of treatment regimens in over half the cohort (52.9%) significantly limit meaningful interpretation of efficacy outcomes and preclude firm conclusions about treatment response. The single case of documented relapse (5.9%) during median follow-up of 18 months is encouraging, though longer follow-up data are

needed to assess durable remission rates and long-term overall survival. It is particularly notable that CNS prophylaxis was administered in only 37.5% of treated patients (n=3 of 8), despite the universal CNS-high-risk profile evident in this cohort with 82.4% CNS involvement at diagnosis.

Study Limitations

Several important limitations of this study warrant explicit acknowledgment. First, the retrospective nature and modest sample size (n=17) limit statistical power for robust prognostic analysis and subgroup comparisons. Second, the exceptionally high frequency of CNS and bone marrow involvement (82.4% each) raises significant concerns about potential misclassification or differential ascertainment bias, necessitating prospective validation in larger, independent cohorts before firm conclusions can be drawn. Third, cell-of-origin classification was not fully characterized in all cases (17.6% incomplete), limiting molecular subtype analysis. Fourth, the single-center design may not generalize to other geographic or healthcare settings. Finally, the limited median follow-up duration (18 months, range 3-42 months) precludes definitive assessment of long-term overall survival and disease-free survival rates. These limitations must be considered when interpreting the study findings.

CONCLUSION

This case series documents gastric DLBCL presenting with an aggressive disease phenotype, extensive extra-nodal dissemination, and advanced-stage disease at presentation in a South Asian tertiary care center. Key findings include:

- 1) Younger median age at presentation (48.7 years; 70.6% <60 years) compared to Western cohorts;
- 2) Profound hematologic abnormalities including anemia in 94.1% and hypoalbuminemia in 88.2%;
- 3) Remarkably high extra-nodal involvement (CNS 82.4%, bone marrow 82.4%) substantially exceeding published literature;
- 4) Higher-than-expected double-expressor prevalence (17.6%);
- 5) Favorable initial treatment response (87.5% ORR with R-CHOP) despite incomplete treatment documentation and limited follow-up;
- 6) Low relapse rate (5.9%) during the available follow-up period.

The extraordinarily high frequencies of CNS and bone marrow involvement in this cohort warrant prospective validation in larger, independent cohorts to distinguish between true epidemiological differences versus diagnostic or classification artifacts. Future studies should employ standardized staging protocols, uniform treatment documentation, and extended follow-up (minimum 3-5 years) to better characterize this disease in South Asian populations. Comprehensive molecular profiling with gene expression analysis and whole-exome sequencing may elucidate the aggressive biology observed in this cohort and identify potential therapeutic targets.

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