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#1029 - Tertiary Lymphoid Structures are Scarce but Associated with BCR Clonal Expansion, B Cell Activity and Checkpoint Inhibitor Response in Advanced Osteosarcoma

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Background

Tertiary lymphoid structures (TLS) have been associated with tumor response to checkpoint inhibitors (ICIs) in total mutation burdeon (TMB)-low cancers such as soft tissue sarcoma and renal clear cell carcinoma. However, its role in bone sarcoma has not been thoroughly investigated.

Here, we aim to explore the presence of TLS in primary as well as recurrent tumor specimens in osteosarcoma and undifferentiated polymorphic sarcoma (UPS) of bone. We also explore the association of TLS with immune-microenvironment and the efficacy of immunotherapy.

Patients and methods

We retrospectively evaluated the presence as well as the location of TLS by histology examination and immunohistochemistry in 103 tumor specimens, including 35 primary lesions and 78 recurrent lesions, including local recurrence (LR, n=13), pulmonary recurrence (n=60), bone metastasis (BM, n=4) and lymph node metastasis (LM, n=1). There were 68 males and 35 females, with a median age of 19 (range 7~79) years old.

Whole transcriptome sequencing (RNA-seq) was performed in 81 specimens to interrogate the immune cell infiltration, B-cell receptor (BCR) repertoire as well B cell activity-related pathways.

Among these patients, the clinical efficacy of PD-1 blockade in 37 subjects were assessed by RECIST 1.1. The therapeutic response of ICIs in relation to the presence of TLS was also investigated.

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All authors — including co-authors — listed on the author string declare no competing interests related to this scientific work

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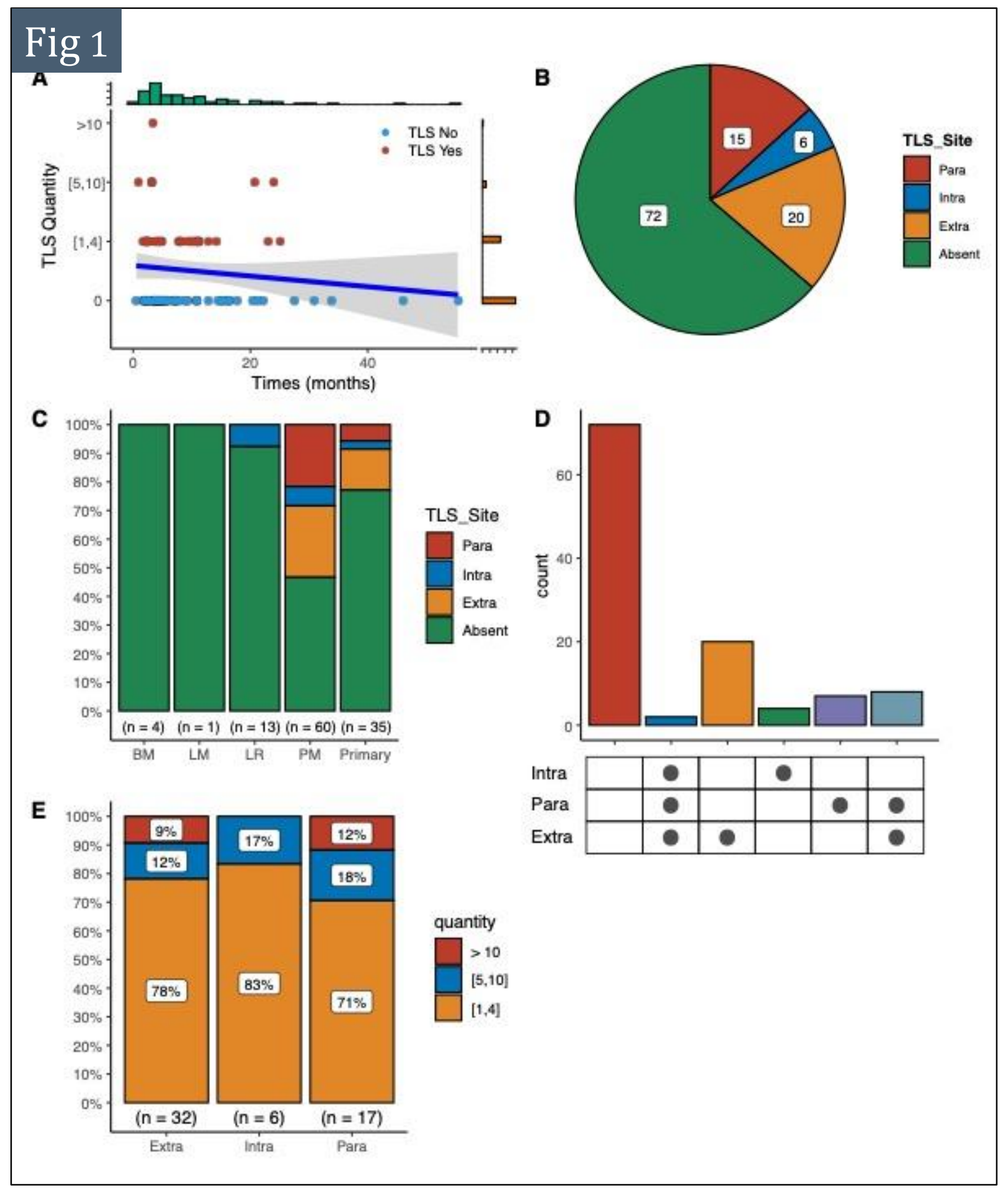
The landscape of TLS in osteosarcoma and UPS of bone

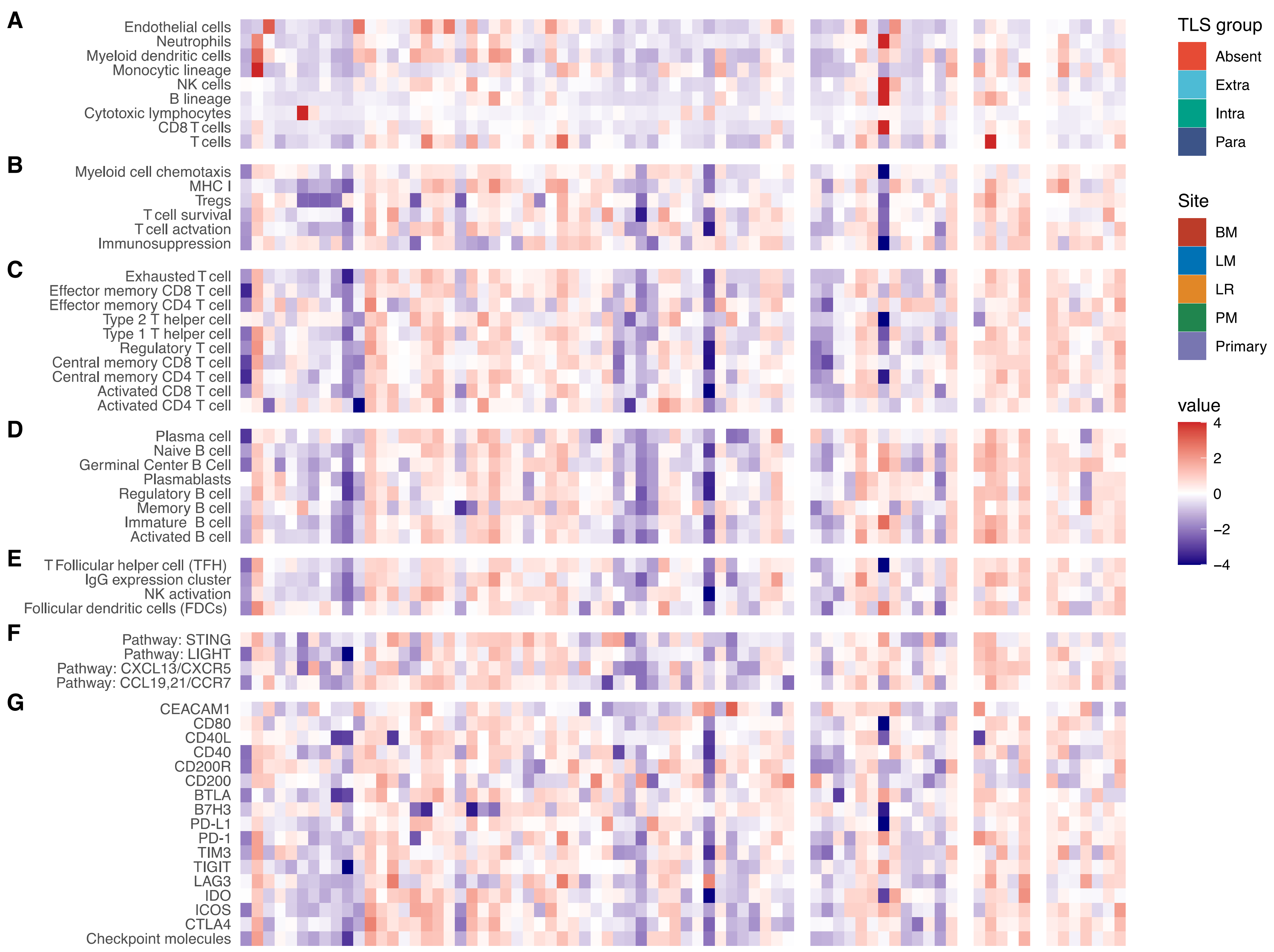
We observed the presence of intra-tumor TLS in 6 (5.8%) samples, peri-tumor TLS in 17 (16.5%), TLS outside the tumor in 32 (31.1%) samples and the total absence of TLS in 49 (46.6%) samples. The vast majority of intra- or peri-tumor TLS formation are observed in pulmonary metastasis, but not primary lesion, LR bone BM or LM. Interestingly, the formation of TLS is relatively common in the first 1.5 years since the diagnosis of tumor recurrence, but rarely seen in specimens obtained after 1.5 years (Fig 1).

Fig 1



In 81 samples with whole transcriptome sequencing result, we observe that there are no significant difference in the major component of immune microenvironment. However, there is a drastic difference in intra-tumor T cell and B cell subtypes, with an enhanced anti-tumor phenotype in specimens intra- and peri-tumor TLS (TLS-present), but not those with extra-tumor or no TLS (TLS-absent) (Fig 2).

Fig 2



While the frequency of TLS formation is in the midst of various pediatric cancers, it remains scarce compared to the most common adult cancer types (Fig 3) such as renal or lung cancer. Interestingly, B cell receptor(BCR) analysis suggest a higher clonality of BCR in specimens with TLS-present tumor compared to TLS-absent counterparts (Fig 4).

In TLS-present tumor specimens, we noticed an up-regulation of TLS formation pathways such as LIGHT, CXCR5/CXCL13 and CCL19,21/CCR7. In comparison with TLS-absent, TLS-present tumors demonstrate a higher expression of common immune checkpoint molecules such as PD-L1, CTLA4, LAG3, B7H3, CD40, etc (Fig 2 bottom).

Fig 3

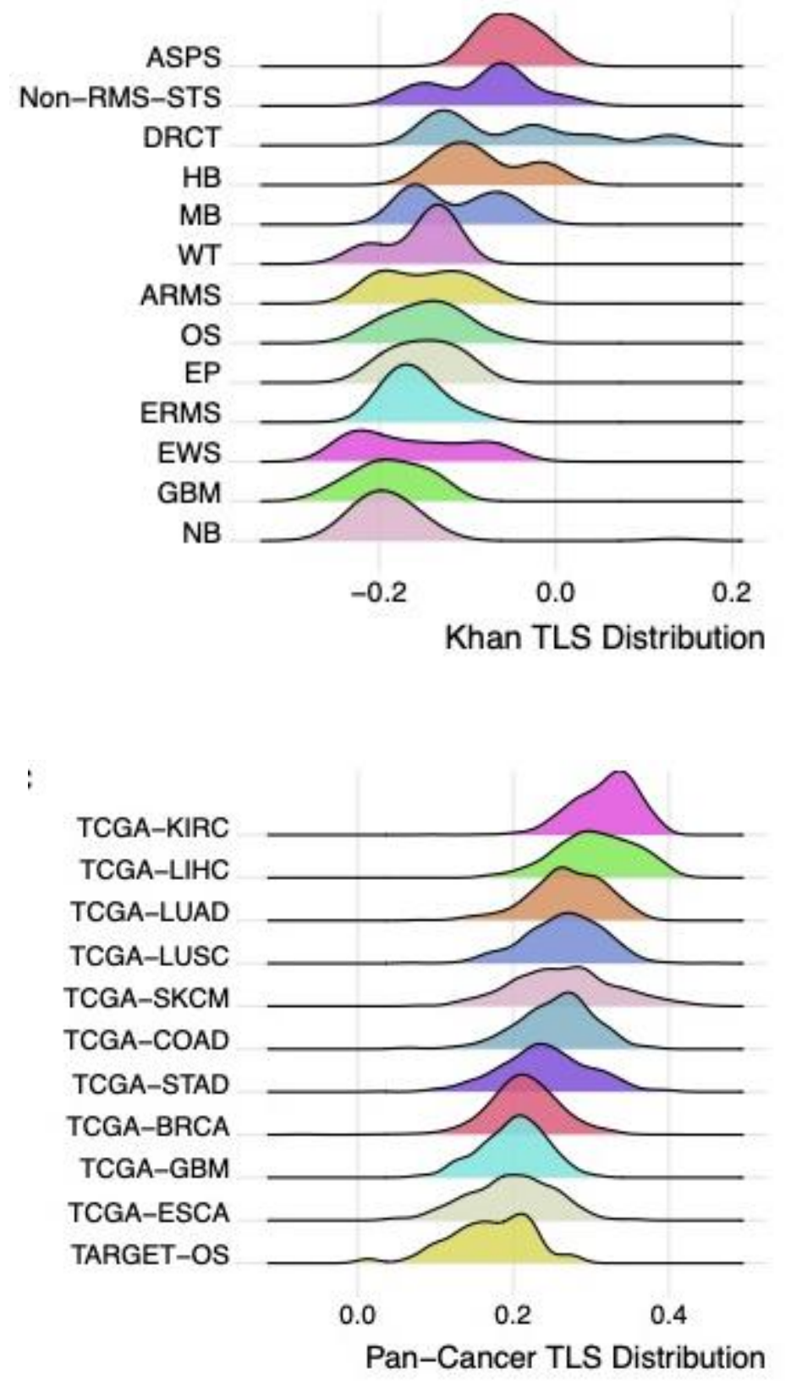
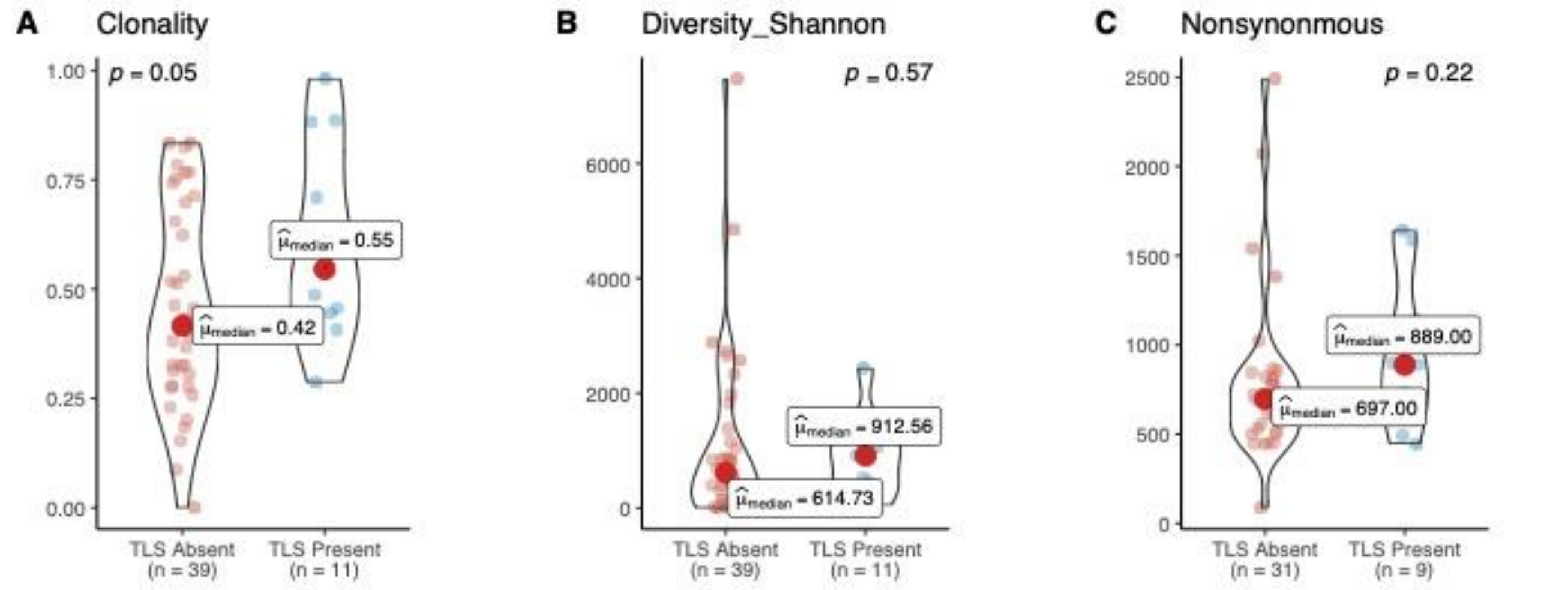


Fig 4

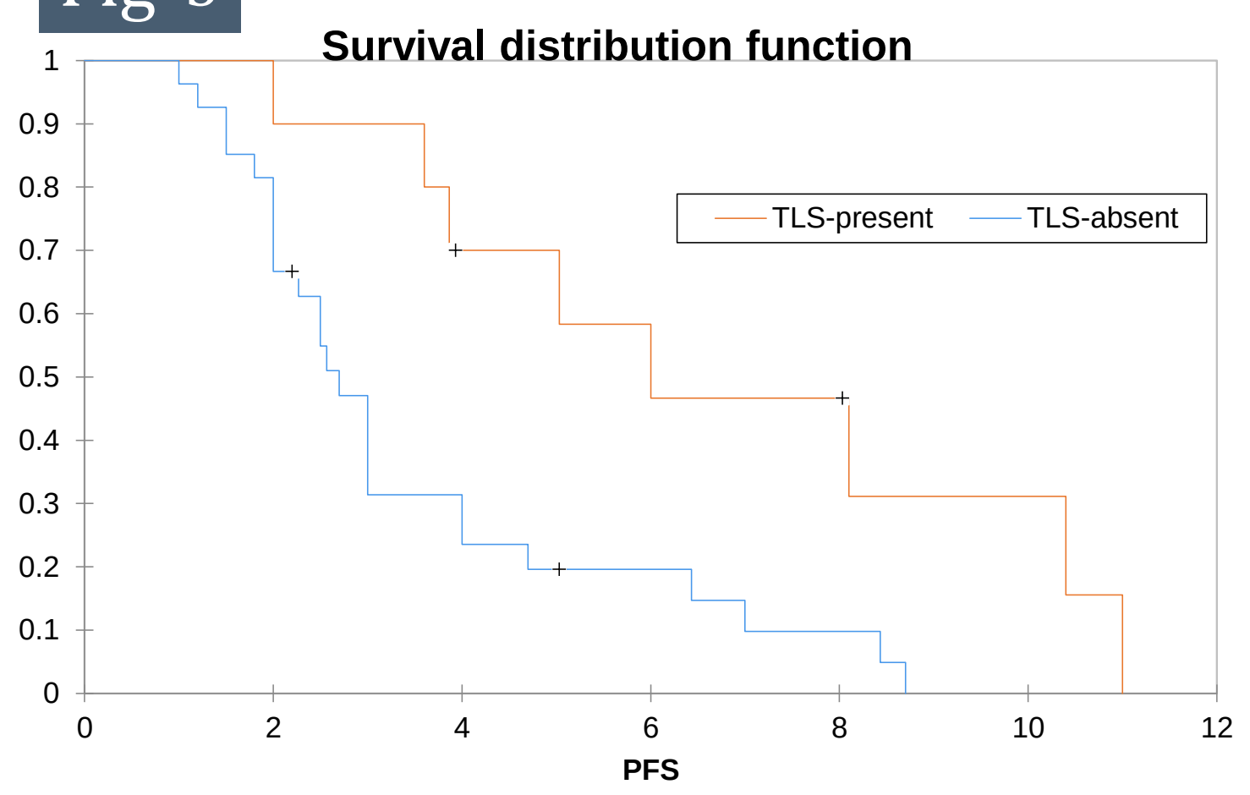


The association of TLS with ICI response

Surprisingly, the median progression-free survival (mPFS) following PD-1 blockade therapy was 6 months in patients (n=10) with TLS-present tumor, yet tremendously shorter in 27 patients of TLS-absent tumor (mPFS=2.6 months) (Fig 5).

Using flow cytometry assay, we also observe a higher percentage of serum CD45RO+CD62L- T cells (effector memory T) with a lower percentage of CD45RA+CD62L+T cells lymphocytes pretreatment in patients with TLS.

Fig 5



Conclusion

Our report depicts the first landscape of TLS in osteosarcoma and UPS of bone. Our result suggests a organ-tropic formation of TLS in pulmonary, but not other sites of recurrent lesions. Furthermore, TLS predicts the efficacy of PD-1 blockade in patients with advanced osteosarcoma which warrant further clinical validation.