Original Article

Clinical prognostic value of TREM1 in patients with liver cancer lung metastasis

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Background: Patients diagnosed with hepatocellular carcinoma (HCC) generally have an unfavorable outlook, with lung metastasis being a prevalent factor contributing to mortality. The metastatic microenvironment is critical to the tumor metastatic process. The exact impact of Triggering Receptor Expressed on Myeloid Cells 1 (TREM1) on tumor metastasis and the microenvironment of metastasis is still not known. By analyzing online databases and a clinical cohort, we evaluated the predictive significance of TREM1 and its correlation with the tumor microenvironment (TME).

Methods: Using the Gene Expression Omnibus (GEO) dataset (GSE141016), genes differentially expressed in liver cancer and lung metastases were analyzed. Data from liver hepatocellular carcinoma (LIHC) of The Cancer Genome Atlas (TCGA) were acquired through RNA sequencing. The abundance of tumor-infiltrating immune cells was estimated using Estimation of Stromal and Immune cells in Malignant Tumor tissues using Expression data (ESTIMATE). The single sample gene set enrichment analysis (ssGSEA) algorithm was utilized to determine the association between TREM1 and immune cells. The level of TREM1 and immune cells were determined in formalin-fixed paraffin-embedding (FFPE) specimens.

Results: Increased expression of TREM1 in HCC was linked to a poorer clinical prognosis and elevated incidence of lung metastasis. Furthermore, TREM1 was found to be associated with multiple immune cells in the TME. We noticed that lung metastases in the same patient had higher levels of TREM1 protein compared to primary liver cancer. Additionally, lung metastases exhibited increased neutrophil numbers and neutrophil extracellular traps (NETs) formation compared to primary liver cancer. Moreover, there was a positive correlation between TREM1 and both neutrophils and NETs.

Conclusions: Increased expression of TREM1 in HCC is linked to a poorer clinical outlook and elevated incidence of lung metastasis, suggesting its potential as a prognostic biomarker for patients with liver cancer lung metastasis.

Keywords: Hepatocellular carcinoma (HCC); lung metastasis; Triggering Receptor Expressed on Myeloid Cells 1 (TREM1); neutrophil; neutrophil extracellular trap (NETs)

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Introduction

Hepatocellular carcinoma (HCC), a highly malignant tumor of the gastrointestinal tract, ranks sixth among the most prevalent cancers globally and has the fourth highest fatality rate (1). Although there has been significant advancement in clinical therapy in recent times, the outlook for individuals with HCC continues to be unfavorable. The primary cause for this grim prognosis is predominantly the occurrence of metastasis, particularly in the lungs (2,3). The metastatic microenvironment is critical to the tumor metastatic process. The metastasis of primary tumors requires a microenvironment favorable to cancer metastasis, called the pre-metastatic niche (4,5). However, research remain to be done on how tumors remodel the pre-metastatic niche.

Neutrophils play a crucial role in the process of tumor metastasis (6). The metastatic microenvironment associated with neutrophils is characterized by the formation of neutrophil extracellular traps (NETs), secretion of pro-tumorigenic factors, and immune modulation (7). Neutrophils have the ability to generate NETs (8,9). NETs trap circulating tumor cells, aiding their adhesion and extravasation into lung tissue initially discovered to ensnare and eliminate invading pathogens (10). Neutrophils secrete cytokines and growth factors that create a supportive microenvironment, suppress other immune cells, and remodel tissue, all of which facilitate early metastasis and colonization of cancer cells in the lungs (11,12). According to recent research, the generation of NETs by neutrophils can induce a cancerous inflammatory reaction, leading to the spread of HCC to the lungs (13). However, the mechanisms involved in cancer cells regulating production of NETs by neutrophils in the metastatic tumor microenvironment (TME) remain unclear.

Triggering Receptor Expressed on Myeloid Cells 1 (TREM1) is an immunogroblin (Ig) superfamily receptor found on bone marrow cells. It has a crucial function in innate immunity by enhancing the inflammatory response (14). Research has indicated that there is a rise in TREM1 levels on the outer layer of tumor associated macrophages (TAMs) in HCC, resulting in a suppression of the immune system (15). In addition, TREM1 also promotes HCC cell proliferation by regulating the phosphorylation of AKT, STAT3 and p65 (16,17). Nevertheless, the impact of TREM1 on the metastatic TME and its role in tumor metastasis remains unexplored.

This study validated the clinical importance of TREM1 in HCC and additionally investigated the correlation between TREM1 and the spread of cancer to the lungs in liver cancer cases. Furthermore, our study explored the control of TREM1 in immune cells within the metastatic TME and revealed the potential pathway through which HCC enhances TREM1 expression, consequently influencing the formation of NETs in metastatic sites and facilitating the spread of liver cancer to the lungs. These findings offer potential novel treatment strategies for patients with HCC. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-492/rc).

Highlight box

Key findings

- Increased expression of Triggering Receptor Expressed on Myeloid Cells 1 (TREM1) in hepatocellular carcinoma is linked to a poorer clinical outlook and elevated incidence of lung metastasis.

What is known and what is new?

- Neutrophil extracellular traps (NETs) produced by neutrophils facilitate the metastasis of tumor cells.
- In liver cancer with lung metastasis, TREM1 is associated with NETs and is related to clinical prognosis.

What is the implication, and what should change now?

- This study identifies TREM1 as a potential new target for predicting and treating tumor metastasis.

Methods

Human tissues

Analysis was conducted using a tumor microarray (TMA) obtained from 80 patients with HCC, along with follow-up data. Seventeen samples of primary liver tumors and lung metastases were obtained from Shanghai Renji Hospital. This study was performed in line with the principles of the Declaration of Helsinki (as revised in 2013). Ethical approval from the ethical review committees of Shanghai Renji Hospital, Shanghai Jiao Tong University was obtained for the study (No. 2021-101). Informed consent was obtained from all individual participants included in the study.

Online data acquisition and analyses

Using the Gene Expression Omnibus (GEO) dataset (GSE141016 and GSE40367), we conducted a comparative analysis of gene expression between primary liver cancer

(n=31) and lung metastases (n=31). RNA sequencing data were collected from liver hepatocellular carcinoma (LIHC) in The Cancer Genome Atlas (TCGA) database (374 liver cancer, n=374; and normal tissues, n=50). Patients with HCC were categorized into high and low groups based on TREM1 level, and subsequently, separate analyses were conducted to assess overall survival (OS) and progression-free survival (PFS). To evaluate the level of immune cell infiltration in the tumor, gene expression profiles were utilized for assessing the abundance of immune cell infiltration using ESTIMATE. The single sample gene set enrichment analysis (ssGSEA) algorithm was utilized to compute the correlation between TREM1 and the expression of genes in immune cells. Gene sets that had a standardized P value <0.05 and a false discovery rate P value <0.05 were considered as positive gene sets.

Immunofluorescence (IF) staining and immunohistochemistry (IHC) staining

The test was conducted following the previously mentioned procedure (18). Formalin-fixed paraffin-embedding (FFPE) tissue sections underwent deparaffinization in xylene and rehydration in a series of graded alcohol solutions. Antigen retrieval was achieved by microwave treatment in citrate buffer (pH: 6.0). Subsequently, non-specific binding sites were blocked with 5% bovine serum albumin in phosphate-buffered saline (PBS) at room temperature for 1 hour. The tissue sections were incubated with a primary antibody overnight at 4 ℃, followed by washing with PBS and incubation with the appropriate fluorescently conjugated secondary antibody for 1 hour at room temperature. Nuclei were counterstained with 4',6-diamidino-2-phenylindole (DAPI). The primary anti TREM1 antibody (Abcam, Cambridge, UK, Cat# ab86490) was used for IHC staining (dilution ratio 1:200). IF staining was performed using the primary anti-myeloperoxidase (MPO) antibody (Thermo Fisher Scientific, Waltham, USA, Cat# MA1-10439) at a dilution of 1:100, along with the anti-citH3 antibody (Abcam, Cat# ab5103) at the same dilution.

Multiplex immunohistochemistry (mIHC) staining

The fluorescent dye experiments were conducted following the previously provided procedure (19) with the utilization of anti-human antibodies for CD11c, CD86, CD206, CD66b, CD14, CD11b, CD19, CD8, CD4, Foxp3, and CD56 (Abcam). We utilized the PerkinElmer (Waltham, USA) Vectra3® system to scan the slides and measure the outcomes.

Statistical analyses

GraphPad Prism 7.0 (La Jolla, CA, USA) was utilized for the analyses. We utilized Student's *t*-tests to analyze the variances between the two groups. Correlations were analyzed using Pearson's correlation test, while univariate analysis was performed using the *t*-test. Statistical significance was determined using the log-rank test on the follow-up data, with P values less than 0.05 being considered significant.

Results

TREM1 associates with a worse clinical outcome

In order to identify the main genes linked to liver cancer's lung metastases, we conducted a differential gene analysis on the primary liver cancer and lung metastases using the GEO dataset (GSE141016) (*Figure 1A*). We found that TREM1 was a significantly upregulated gene in lung metastases. Consistently, we analyzed another GEO dataset (GSE40367) and found that TREM1 was upregulated in lung metastases (Figure S1). In order to investigate the correlation between TREM1 and clinical prognosis, we examined the association between TREM1 and patient prognosis in the LIHC dataset of the TCGA database. Our findings indicate that the group with high levels of TREM1 exhibited poorer OS and PFS outcomes (*Figure 1B,1C*). In our analysis of a liver tumor group, we consistently observed that increased expression of TREM1 in HCC patients was linked to poorer OS, survival without metastasis, and survival without lung metastasis (*Figure 1D-1F*). In addition, TREM1 expression was lower in tumors than in normal liver tissues according to TCGA data (*Figure 1G*). Protein levels and mRNA levels of TREM1 were consistent, and *Figure 1H,1I* demonstrate the protein levels of TREM1 in HCC and in normal liver tissues.

TREM1 promotes liver cancer lung metastasis

In order to examine the correlation between TREM1 and metastasis of liver cancer, we analyzed the levels of TREM1 in different groups of patients within the liver cancer cohort. Our findings revealed that the proportion of patients with high and medium levels of TREM1 was significantly higher in those with extrahepatic and lung metastasis compared

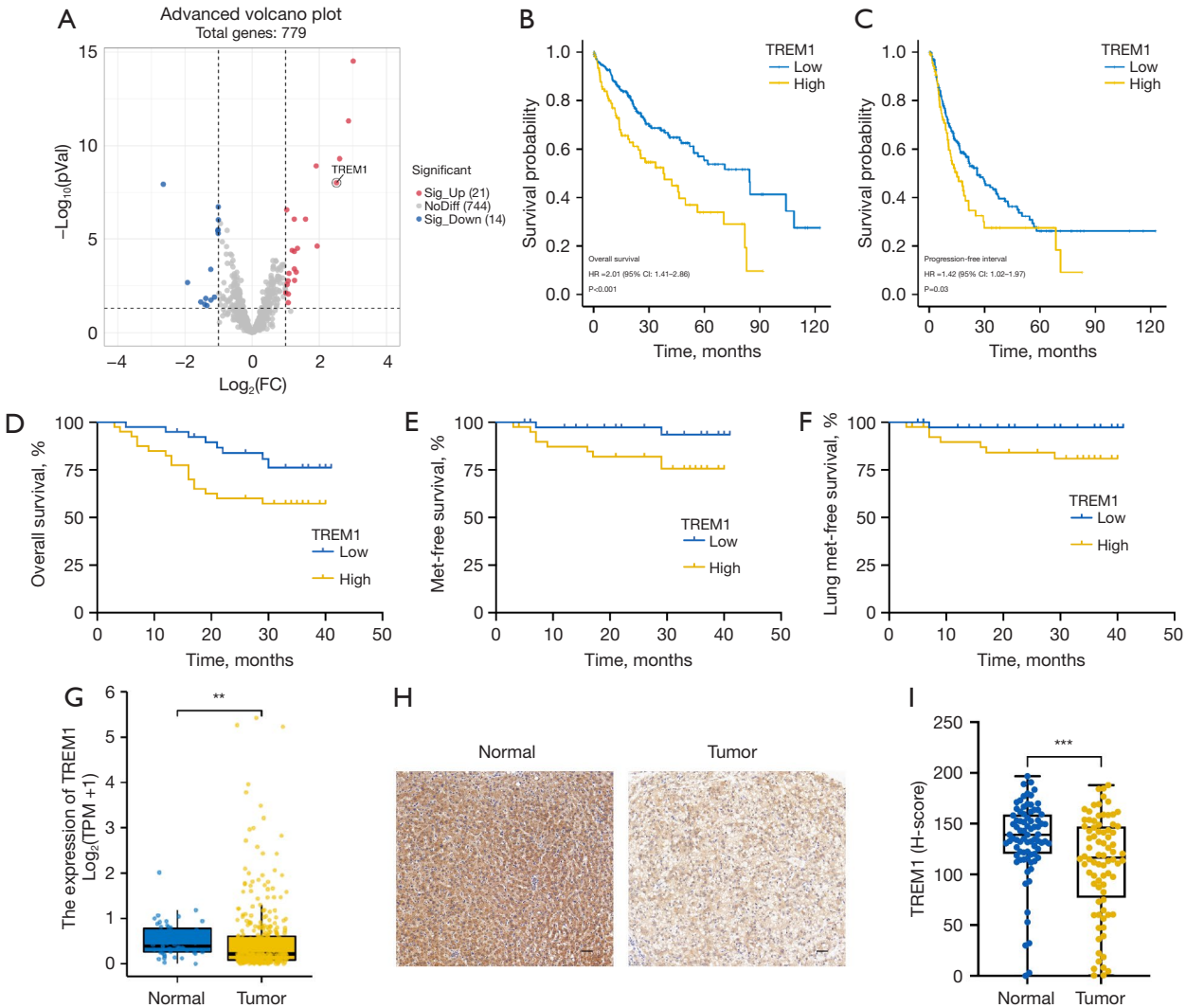

Figure 1 TREM1 associates with a worse clinical outcome. (A) Volcano plots of differential gene expression in 31 patients with paired primary tumors and lung metastases. Blue and red dots represent downregulated and upregulated genes, respectively. (B,C) TREM1 expression analysis of LIHC from TCGA. (B) Overall survival and (C) Progression-free interval of TREM1 high group and TREM1 low group. (D-F) TREM1 expression analysis of a liver cancer cohort from Shanghai Renji Hospital (n=80). (D) Overall survival, (E) met-free survival and (F) lung met-free survival. (G-I) TREM1 expression level analysis of liver cancer (G) patients from TCGA, and (H,I) IHC staining of TREM1 in liver cancer and normal liver tissues from Shanghai Renji Hospital (n=80). Scale bars, 50 μm. **, P<0.01; ***, P<0.001, by log rank test (B-F) and two-tailed unpaired *t*-test (G,I). FC, fold change; TREM1, Triggering Receptor Expressed on Myeloid Cells 1; HR, hazard ratio; CI, confidence interval; TPM, transcripts per million; LIHC, liver hepatocellular carcinoma; TCGA, The Cancer Genome Atlas; IHC, immunohistochemistry.

to patients without any metastasis (*Figure 2A,2B*). In the *Figure 2C*, it can be observed that the levels of TREM1 protein were consistently elevated in patients who experienced extrahepatic metastases and lung metastases compared to patients who did not have any metastases. No significant correlation was observed between the expression of TREM1 and tumor size or recurrence rate, however, the TREM1 high group exhibited higher rates of extrahepatic and lung metastasis compared to the TREM1 low group (*Figure 2D*). Moreover, examination of the levels of TREM1 protein in primary liver cancer and lung metastases from the identical patient revealed a notable increase in TREM1

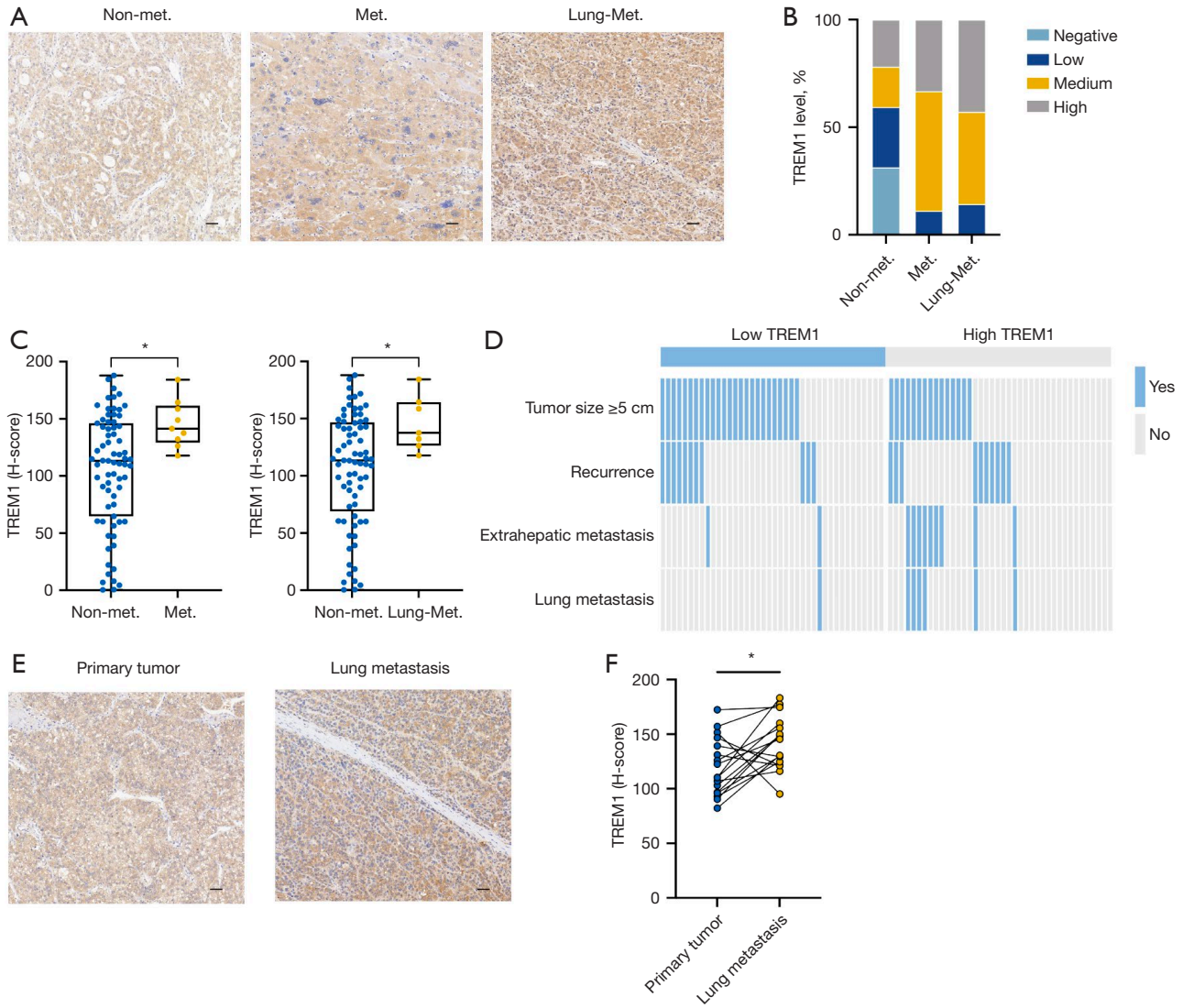

Figure 2 TREM1 promotes liver cancer lung metastasis. (A-C) IHC staining of TREM1 in non-metastasis (n=69), extrahepatic metastasis (n=11) and lung metastasis (n=7). (A) Representative pictures of TREM1 IHC staining. (B) Composition of TREM1 expression level in non-metastasis, extrahepatic metastasis and lung metastasis. (C) Comparison of TREM1 between non-metastasis and extrahepatic metastasis, non-metastasis and lung metastasis, respectively. (D) Clinical events of TREM1 high group (n=40) and TREM1 low group (n=40). (E,F) Comparison of TREM1 between paired primary tumors and lung metastases. (E) Representative pictures of TREM1 IHC staining and (F) statistics chart. Scale bars, 50 μm. *, P<0.05, by Chi-squared test (D) and two-tailed unpaired (C) or paired (F) *t*-test. met., metastasis; TREM1, Triggering Receptor Expressed on Myeloid Cells 1; IHC, immunohistochemistry.

expression in the lung metastases compared to the primary liver cancer (*Figure 2E,2F*).

TREM1 associates with tumor immune microenvironment

By utilizing the ESTIMATE package, we assessed the ESTIMATE score, Immune score, and Stromal score based on the TCGA database to determine if TREM1 plays a role in tumor metastasis through immune microenvironment reprogramming. Our findings revealed that the TREM1 high group exhibited elevated ESTIMATE score, Immune score, and Stromal score compared to the TREM1 low group (*Figure 3A*). In order to further examine the impact of TREM1 on the immune microenvironment

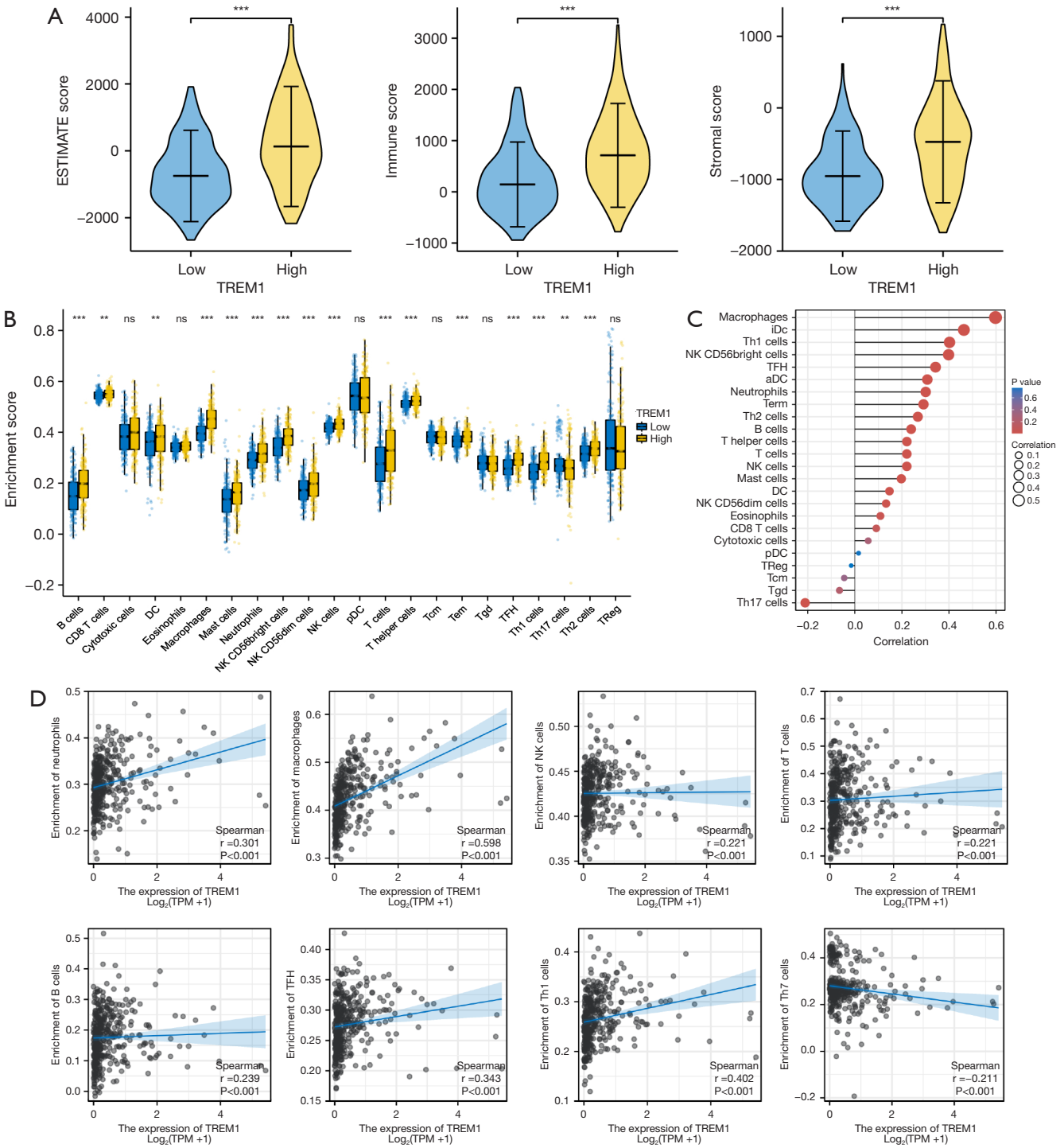

Figure 3 TREM1 associates with tumor immune microenvironment. (A) Violin plots show ESTIMATE score, Immune score and Stromal score of TREM1 high and low group from TCGA. (B-D) Analyses of TREM1 expression and immune infiltration in LIHC of TCGA. (B) Enrichment score of infiltration profile of immune subsets based on TREM1 expression levels from TCGA using ssGSEA. (C) Lollipop plots show correlation between TREM1 and immune infiltration in LIHC of TCGA using ssGSEA. (D) Correlation analysis of TREM1 and immune cells from TCGA using ssGSEA. **, P<0.01; ***, P<0.001; ns, not significant, by two-tailed unpaired *t*-test and Pearson correlation analysis. ESTIMATE, Estimation of Stromal and Immune cells in Malignant Tumor tissues using Expression data; TREM1,

Triggering Receptor Expressed on Myeloid Cells 1; DC, dendritic cells; NK, natural killer; pDC, plasmacytoid dendritic cells; TFH, T follicular helper cells; iDC, immature dendritic cells; aDC, activated dendritic cells; TPM, transcripts per million; TCGA, The Cancer Genome Atlas; LIHC, liver hepatocellular carcinoma; ssGSEA, single sample gene set enrichment analysis.

of tumors, we utilized the TCGA database to investigate the relationship between TREM1 and immune cells. Our findings revealed that the group with high levels of TREM1 exhibited increased quantities of B cells, $CD8^+$ T cells, dendritic cells (DC), macrophages, mast cells, neutrophils, natural killer (NK) cells, T cells, Tem cells, T follicular helper cells (TFH), Th1 cells, and Th2 cells, while displaying lower level of Th17 cells in comparison to the group with low level of TREM1 (*Figure 3B*). TREM1 exhibited positive correlations with macrophages, DC, Th1 cells, neutrophils, Tem, TFH, B cells, NK cells, and mast cells, while displaying a negative correlation with Th17 cells (*Figure 3C*). Furthermore, our analysis using the ssGSEA algorithm revealed a positive correlation between TREM1 and neutrophils, macrophages, NK cells, T cells, B cells, TFH and Th1 cells, while showing a negative correlation with Th17 cells (*Figure 3D* and Figure S2).

TREM1 promotes neutrophil in lung metastasis

In order to further explore the connection between TREM1 and the immune microenvironment of tumors, we utilized fluorescent mIHC to analyze immune cells associated with metastasis in liver cancer and lung metastasis tissues obtained from the identical patient (*Figure 4A-4C*). The number of neutrophils, M1, $CD4^+$ T and Treg cells increased and the number of NK cells decreased in lung metastases compared to the primary liver cancer foci (*Figure 4D* and Figure S3). Furthermore, we investigated the association between TREM1 and immune cells and discovered a positive correlation between TREM1 and neutrophil (r=0.3740, P=0.02) as well as M1 (r=0.3661, P=0.03) (*Figure 4E* and Figure S4).

TREM1 regulates liver cancer lung metastasis by NETs forming

We next found that TREM1 regulation of liver cancer lung metastasis was associated with neutrophils and NETs in metastatic microenvironment. Prior research has indicated that cancer cells have the ability to stimulate neutrophils into generating NETs. In our study, we conducted IHC and IF staining on primary tumor and lung metastasis tissue samples obtained from the same patient. Our findings revealed that the lung metastases exhibited a greater abundance of neutrophils and a higher level of NETs compared to the primary liver cancer (*Figure 5A,5B*). After examining the relationship between TREM1 and neutrophils and NETs, we discovered a positive correlation between TREM1 and both neutrophils and NETs (*Figure 5C*).

Discussion

The spread of cancer is a complicated procedure that includes various cellular and extracellular elements (20). Metastasis of tumors is influenced not only by the inherent properties of cancer cells, but also by the microenvironment in which they spread (21,22). Cancer cells and metastatic microenvironment are interacting and dynamically changing with each other (23). According to reports, primary tumors have the ability to modify the pre-metastatic environment prior to metastasis, creating a conducive environment for the spread of cancer cells (24). Initially, we discovered TREM1 and through the examination of a group of patients, we observed a notable reduction in the expression levels of TREM1 in HCC tissues compared to normal liver tissues. Additionally, we noted a higher likelihood of lung metastases development in patients exhibiting elevated levels of TREM1 expression. Furthermore, it was noted that the levels of TREM1 were considerably elevated in pulmonary metastases compared to the original liver cancer. Further investigation is needed to explore the underlying causes for the heightened expression of TREM1 in HCC. In our analysis of the relationship between TREM1 and various immune cells in the TME, we discovered a positive correlation between TREM1 and $CD8^+$ T cells, dendritic cells, macrophages, mast cells, neutrophils, natural killer cells, T cells, memory T cells, T follicular helper cells, Th1 cells, and Th2 cells. Conversely, we observed a negative correlation between TREM1 and Th17 cells. The results indicate that liver cancer could enhance its own spread by modifying the environment of metastasis using TREM1.

NETs play a crucial role in various physiological and pathological processes (25). In inflammatory and autoimmune diseases, excessive NET formation can cause tissue damage and perpetuate chronic inflammation (26,27).

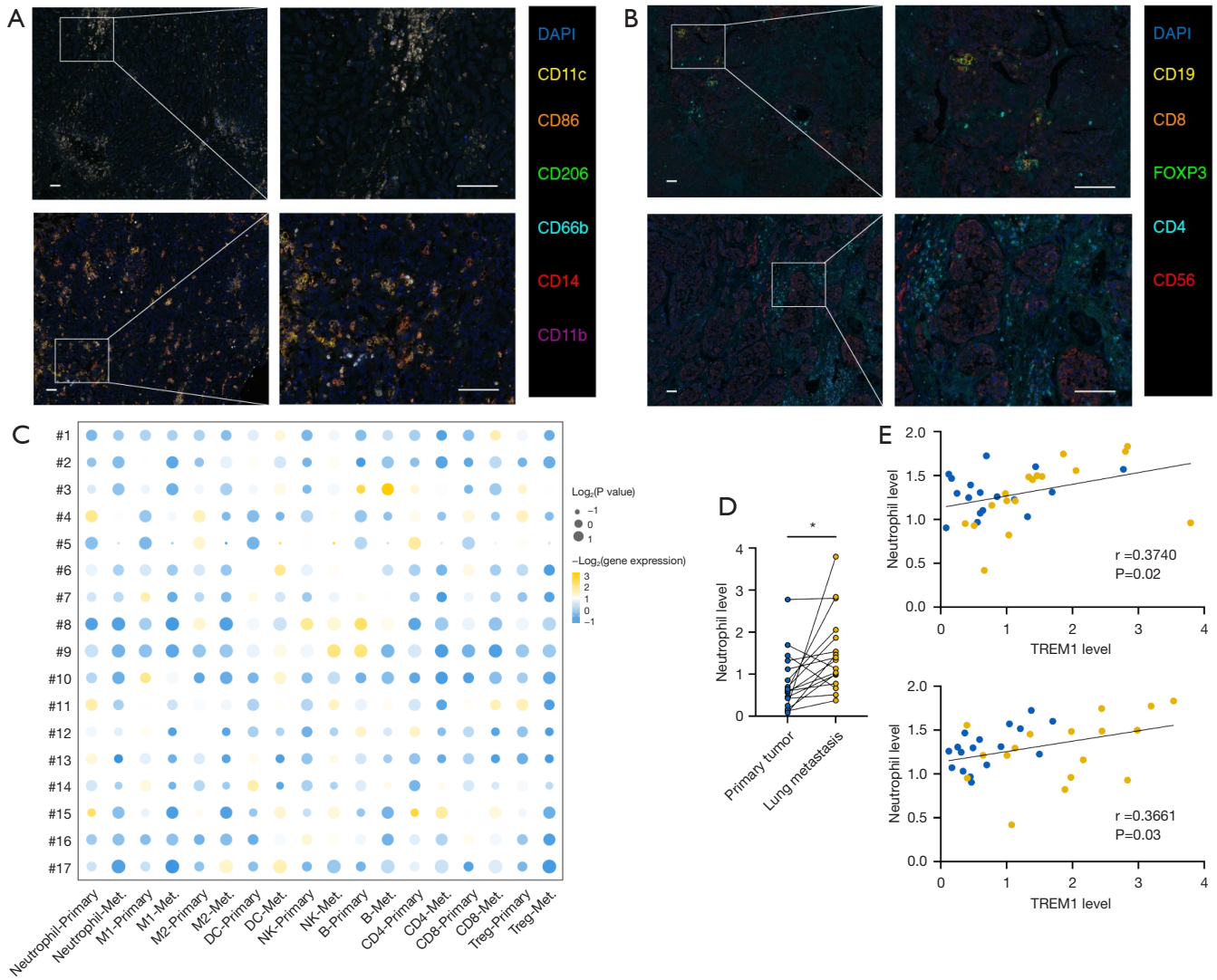

Figure 4 TREM1 promotes neutrophil in lung metastasis. (A-E) Analyses of TREM1 expression and immune infiltration in paired primary tumors and lung metastases form the same patients (n=17) by mIHC staining of metastasis-associated myeloid and lymphatic immune cells. Representative mIHC staining images of metastasis-associated (A) myeloid and (B) lymphatic immune cells. Scale bars, 50 μm. (C) Dot plots displaying TREM1 expression level and altered immune cells in paired primary tumors and lung metastases. (D) Neutrophils analyses between paired primary tumors and lung metastases. (E) Correlation analyses between TREM1 and metastasis-associated immune cells. *, P<0.05, by two-tailed paired *t*-test (D) and Pearson correlation analysis (E). DAPI, 4',6-diamidino-2-phenylindole; Met., metastasis; DC, dendritic cells; NK, natural killer; TREM1, Triggering Receptor Expressed on Myeloid Cells 1; mIHC, multiplex immunohistochemistry.

In immune protection, NETs trap and neutralize pathogens. NETs produced by neutrophils capture and kill pathogens in infection and inflammation (28). In cancer, NETs facilitate tumor progression and metastasis by trapping circulating tumor cells, aiding their adhesion and extravasation, and creating a pro-tumorigenic microenvironment (29,30). While tumor-associated inflammation can stimulate NETs formation, the mechanisms by which tumor cells regulate NETs formation in the non-infected state are poorly understood.

TREM1 was first found in neutrophils, later in macrophages and endothelial cells (31,32). TREM1 is an

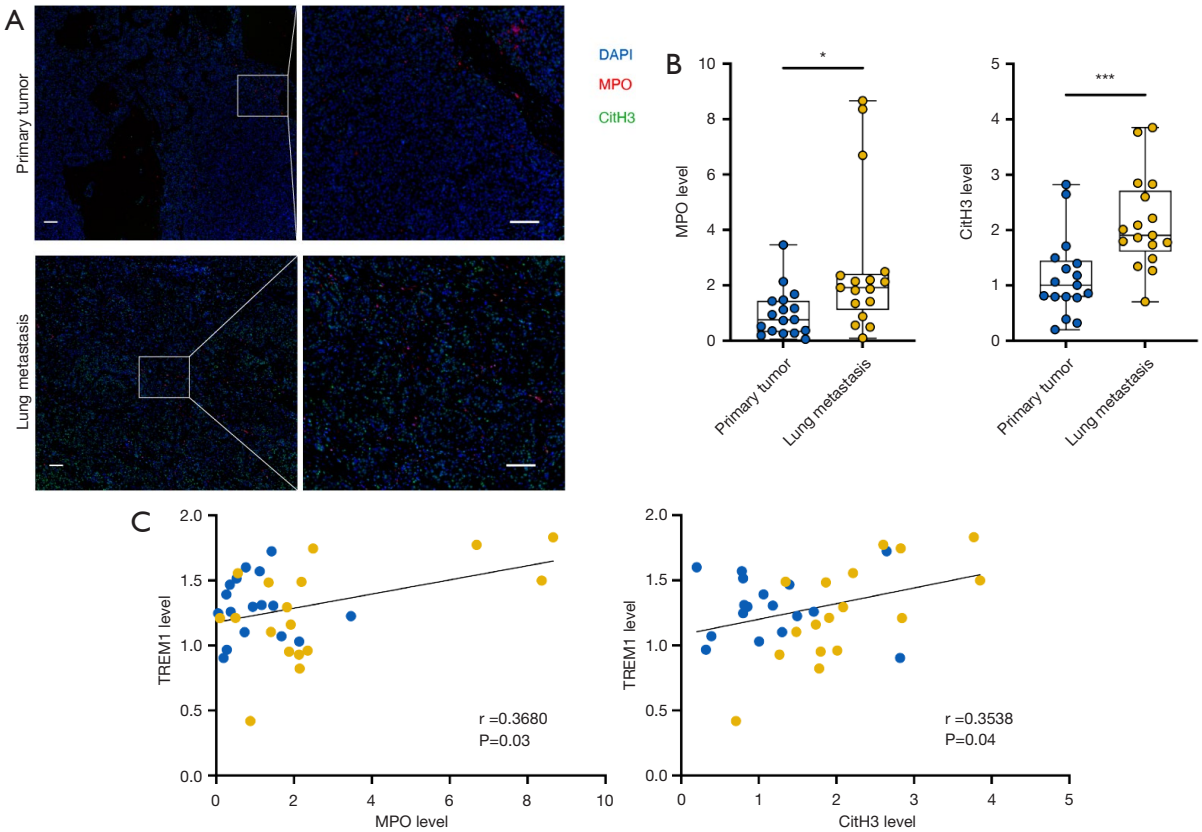

Figure 5 TREM1 regulates liver cancer lung metastasis by NETs forming. (A-C) IHC analysis of TREM1 expression and IF analysis of MPO and CitH3 level in paired primary tumors and lung metastases (n=17). (A) Representative pictures of MPO and CitH3 IF staining. (B) Comparisons of MPO and CitH3 level in primary and metastatic tumors from the same patient. (C) Correlation analysis of TREM1 expression with MPO and CitH3 level. Scale bars, 50 μm. *, P<0.05; ***, P<0.001, by two-tailed unpaired *t*-test (B) and Pearson correlation analysis (C). DAPI, 4',6-diamidino-2-phenylindole; MPO, myeloperoxidase; TREM1, Triggering Receptor Expressed on Myeloid Cells 1; NETs, neutrophil extracellular traps; IHC, immunohistochemistry; IF, immunofluorescence.

inflammatory trigger that induces the release of multiple cytokines and induces an inflammatory response (33). Recent studies have found TREM1 to be associated with macrophage polarization (34), and in addition, the relevance of TREM1 to NETs formation has been reported in sepsis (35,36). However, this is the first report of TREM1 in relation to NETs formation during tumor metastasis. Previous studies indicate that activation of TREM1 on neutrophils induces intracellular signaling pathways, including AKT, STAT5, p38, and ERK1/2, leading to degranulation, calcium flux, and reactive oxygen species (ROS) release. These processes contribute to NETs formation (37). Through IF staining of matched tumor tissues derived from the liver and lungs of the identical patient, it was observed that the quantity of neutrophils and NETs was greater in lung metastases compared to primary liver cancer. Additionally, a positive association was identified between TREM1 and the number of neutrophils within the metastatic TME. Further investigation unveiled a similar positive correlation between TREM1 and NETs generated by neutrophils. Nevertheless, there was also an observed positive correlation between TREM1 and M1 cells in tumor tissues of patients, necessitating additional investigations to elucidate the potential impact of TREM1 on other immune cells within the microenvironment and their respective functions.

This study revealed that increased TREM1 expression in liver cancer was linked to a poorer clinical outlook and elevated incidence of lung metastasis. Furthermore, we found a correlation between TREM1 and multiple immune cells. Higher levels of TREM1 protein were observed in lung metastases compared to primary liver cancer in

paired tissues from the same patient. Additionally, lung metastases exhibited increased neutrophil numbers and NETs formation compared to primary liver cancer. TREM1 showed a positive correlation with both neutrophils and NETs, indicating that tumors may influence the metastatic TME via TREM1 regulation. This implies that liver tumors might control the recruitment of neutrophils and the formation of NETs in the microenvironment of metastatic tumors by means of TREM1, thus impacting the process of lung metastasis in liver cancer. The data validate the possibility of TREM1 as a predictive indicator and treatment objective. The development of potential strategies for treating metastatic tumors will be made easier.

Conclusions

In summary, our study reveals that increased TREM1 expression in HCC is linked to poorer clinical outcomes and higher lung metastasis incidence. TREM1 correlates with various immune cells, particularly neutrophils, and promotes the formation of NETs, aiding tumor cell metastasis. These findings suggest that TREM1 could serve as a prognostic biomarker and a potential therapeutic target in liver cancer with lung metastasis.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-492/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-492/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-492/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was performed in line with the principles of the Declaration of Helsinki (as revised in 2013). Ethical approval from the ethical review committees of Shanghai Renji Hospital, Shanghai Jiao Tong University was obtained for this study (No. 2021-101). Informed consent was obtained from all individual participants included in the study.

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