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LETTER TO THE EDITOR

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The negative relationship between patients with NSCLC harbored STK11/KEAP1 copy number variation and immune microenvironment infiltration

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To the editor,

Studies have found STK11 mutation resistant to immune checkpoint inhibitors (ICIs) and worse survival in KEAP1 mutant patients compared with wildtype in response to ICIs [1, 2]. It has demonstrated that less immune cell infiltration could be found in patients with non-small cell lung cancer (NSCLC) harbored STK11/KEAP1 mutation, which maybe lead to the resistance or worse survival to immune checkpoint inhibitors (ICIs) [3, 4]. However, there have been no relevant studies investigating the association between STK11/KEAP1 copy number variation and immune microenvironment in patients with NSCLC. In this regard, we aim to interrogate the immune microenvironment in patients with NSCLC harboring STK11/KEAP1 copy number variation.

In the present study, we conducted an analysis by evaluating the immuno-contexture in patients with lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) harboring STK11/KEAP1 copy number variation using TIMER databases [5, 6]. We compared the tumor infiltration immune cells with different copy number variation including deep deletion, arm-level deletion, diploid/normal, arm-level gain, high amplification for KEAP1 and STK11 in LUAD and LUSC. The immune cells tested were primarily responsible for efficacious antitumor immunity, characterized by CD8 + T cell, CD4 + T cell and myeloid dendritic cell.

The results showed that for LUAD, arm level gain of STK11 was associated with debilitated immersion of CD8 + T cell ($P = 0.0062$). And arm level deletion of STK11 was correlated with CD4 + T cell infiltration ($P = 0.0016$). Both arm level deletion ($P = 8.4e{-}06$) and arm level gain ($P = 0.0085$) of STK11 was related with myeloid dendritic cells (Fig. 1A). For LUSC, the association could be found between STK11 arm level gain and CD8 + T cell ($P = 0.034$), between STK11 arm level deletion ($P = 0.023$) and myeloid dendritic cells, between STK11 arm level gain ($P = 0.00033$) and myeloid dendritic cells (Fig. 1B).

As we further explored, the association of KEAP1 deep deletion ($P = 0.027$), arm level deletion ($P = 0.0042$) with CD4 + T cell infiltration was found in LUAD. And arm level deletion ($P = 5.4e{-}06$), arm level gain ($P = 0.063$) of KEAP1 were found to be linked with myeloid dendritic cells in LUAD (Fig. 1C). For LUSC, arm level gain of KEAP1 was associated with relatively less myeloid dendritic cell infiltration, as demonstrated in Fig. 1D.

In conclusion, for the first time, we have demonstrated the existence of dampened immune microenvironment in patients with NSCLC harboring STK11/KEAP1 copy number variation. However, it has to be noted that not all forms of copy number variation are linked with less immune cell immersion. Our study provides new insights into the immunological landscape of NSCLC harboring STK11/KEAP1 copy number variation, with relevance for

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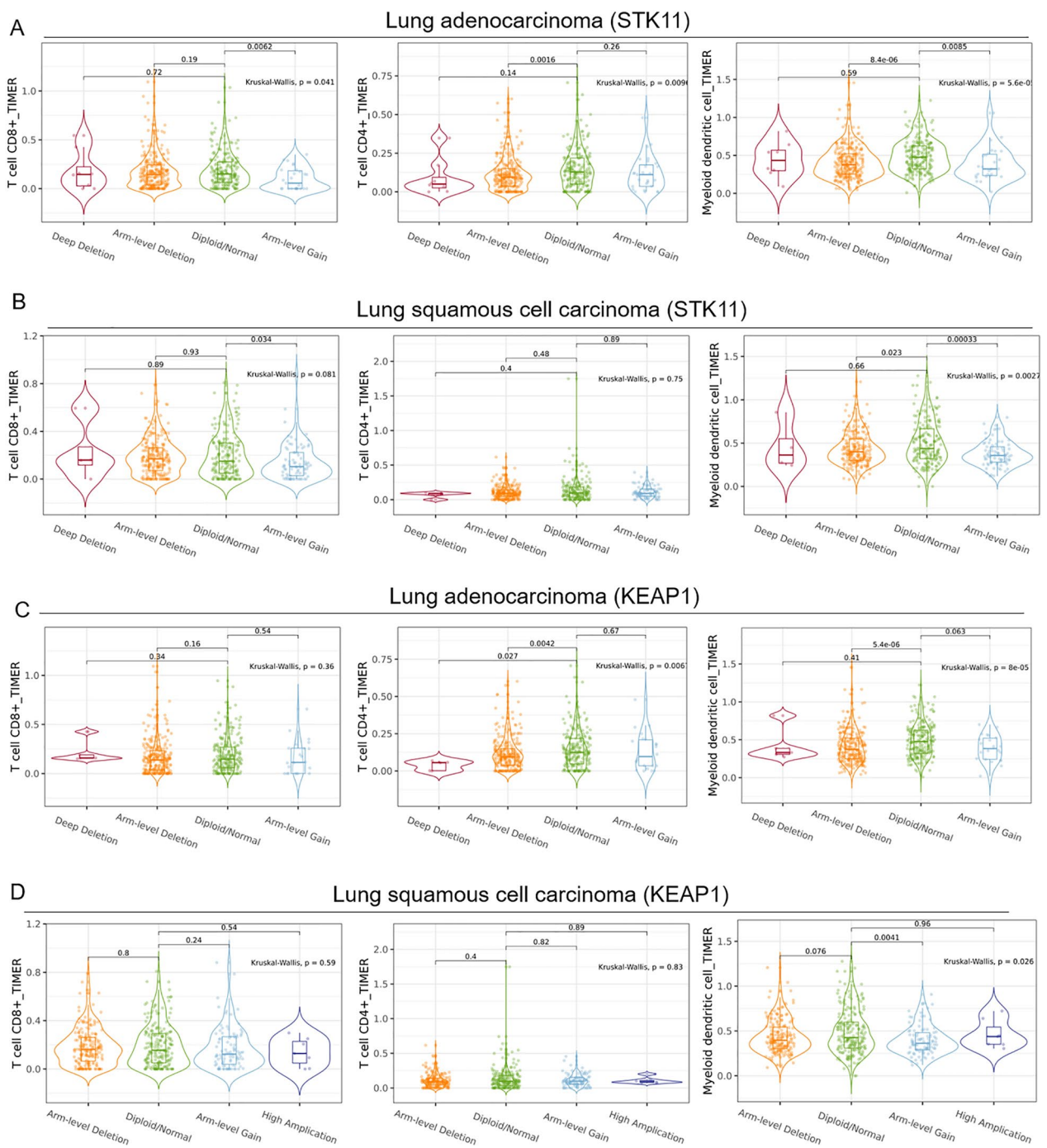

Fig. 1 The association between patients with NSCLC harboring STK11/KEAP1 copy number variation and immune microenvironment infiltration. **A** The association between STK11 copy number alterations (deep deletion, arm-level deletion, diploid/normal, arm-level gain) and the infiltration of immune cells (CD8 + T cell, CD4 + T cells, myeloid dendritic cell) was analyzed in lung adenocarcinoma. **B** The association between STK11 copy number alterations (deep deletion, arm-level deletion, diploid/normal, arm-level gain) and the infiltration of immune cells (CD8 + T cell, CD4 + T cells, myeloid dendritic cell) was analyzed in lung squamous cell carcinoma. **C** The association between KEAP1 copy number alterations (deep deletion, arm-level deletion, diploid/normal, arm-level gain) and the infiltration of immune cells (CD8 + T cell, CD4 + T cells, myeloid dendritic cell) was analyzed in lung adenocarcinoma. **D** The association between KEAP1 copy number alterations (arm-level deletion, diploid/normal, arm-level gain, high amplification) and the infiltration of immune cells (CD8 + T cell, CD4 + T cells, myeloid dendritic cell) was analyzed in lung squamous cell carcinoma

therapeutic intervention. For patients with NSCLC harboring some forms of STK11/KEAP1 copy number variation, little immune cell infiltration is involved. Therefore, more complex treatment strategies may be needed to rekindle immune responses.

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Authors' contributions
CZ designed the study, performed data analysis, wrote the manuscript. The author read and approved the final manuscript.

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Availability of data and materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Since the study is based on public data, the informed consent and ethical proof are not required.

Consent for publication
Not applicable.

Competing interests
The author declared no competing interests.

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