Comprehensive analysis of tumor mutation burden and immune microenvironment in gastric cancer

Jie Yu\(^\dagger\), QianYun Zhang\(^\dagger\), MengChuan Wang\(^a\)\, SiJia Liang\(^c\), HongYun Huang\(^a\), Lang Xie\(^a\), ChunHui Cui\(^a\)\*, JinLong Yu\(^a\)\*

\(^a\) Department of General Surgery, Zhujiang Hospital, Southern Medical University, Guangdong, Guangzhou, 510282, P.R. China.

\(^b\) Department of Medical Ultrasound, Guangzhou Women and Children's Medical Center, Guangdong, Guangzhou, 510623, P.R. China.

\(^c\) Department of Pharmacology, Cardiac and Cerebral Vascular Research Center, Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou, 510080, China.

\(^\dagger\) These authors contributed equally to this work.

* Corresponding Authors:

ChunHui Cui, M.D., Ph.D.
Department of General Surgery, Zhujiang Hospital, Southern Medical University, Guangdong, Guangzhou 510282, P.R. China.
E-mail: drcuich@126.com

JinLong Yu, M.D., Ph.D.
Department of General Surgery, Zhujiang Hospital, Southern Medical University, Guangdong, Guangzhou 510282, P.R. China.
E-mail: yujinlong640506@163.com
ORCID: 0000-0002-4581-1726

Running title: Analysis of TMB and immune microenvironment in gastric cancer.
Abstract

Tumor mutation burden (TMB) was a promising marker for immunotherapy. We aimed to investigate the prognostic role of TMB and its relationship with immune cells infiltration in gastric cancer (GC). We analyzed the mutation landscape of all GC cases and TMB of each GC patient was calculated and patients were divided into TMB-high and TMB-low group. Differentially expressed genes (DEGs) between the two groups were identified and pathway analysis was performed. The immune cells infiltration in each GC patient was evaluated and Kaplan-Meier analysis was performed to investigate the prognostic role of immune cells infiltration. At last, hub immune genes were identified and a TMB prognostic risk score (TMBPRS) was constructed to predict the survival outcome of GC patients. The relationships between mutants of hub immune genes and immune infiltration level in GC was investigated. We found higher TMB was correlated with better survival outcome and female patients, patients with T1-2 and N0 had higher TMB score. Altogether 816 differentially expressed genes were harvested and pathway analysis demonstrated that patients in TMB-high group were associated with neuroactive ligand-receptor interaction, cAMP signaling pathway, calcium signaling pathway. The infiltration of activated CD4+ memory T cells, follicular helper T cells, resting NK cells, M0 and M1 macrophages and neutrophils in TMB-high group were higher compared than that in TMB-low group and high
macrophage infiltration was correlated with inferior survival outcome of GC patients. Last, the TMBPRS was constructed and GC patients with high TMBPRS had poor prognosis.

**Keywords:** Gastric cancer (GC); Tumor mutation burden (TMB); Immune cells infiltration; Prognosis.
Background

According to the statistics in 2018, over 1 million newly diagnosed cases and almost 800,000 cancer-related death making gastric cancer (GC) one of the most intractable diseases worldwide. Overall, gastric cancer ranked third in terms of incidence and 5th in terms of mortality (1). The only curative measure for GC patients is surgery (2). However, most of the cases diagnosed in advanced stage making complete resection impossible (3). The prognosis of GC patients also partially decided by whether lymph nodes were involved (4). Chemotherapy before or after surgery was proved to increase the benefit of patients. Besides, monoclonal drugs target human epidermal growth factor receptor 2 (HER2) and vascular endothelial growth factor receptor 2 (VEGFR2) has also been applied in the clinical practice (5).

Recently, immunotherapy emerged as a rising star in the cancer treatment. The measures consist mainly of immune checkpoint inhibitors (ICIs), cancer vaccines, adoptive T-cell transfer therapy and cytokine therapy (6, 7). Major breakthrough was accomplished by immunotherapy so far. A phase 2 trial revealed that nivolumab (anti-PD-1 monoclonal antibody) plus ipilimumab (anti-CTLA-4 monoclonal antibody) could benefit the patients of malignant pleural mesothelioma (8). The combination of nivolumab and ipilimumab therapy showed promising result in metastatic melanoma patients, especially...
in patients with negative expression of PD-L1(9). Chimeric antigen receptor (CAR) T cells therapy significantly changed the landscape of lymphoma therapy, improving the remission rate of lymphoma patients(10, 11). In addition, CAR-T therapy also offered potential benefit to pancreatic cancer patients(12). A randomized clinical trial demonstrated that cancer vaccine in combination with docetaxel could remarkably enhanced the progression-free survival of metastatic breast cancer patients(13).

It is worth noting that immunotherapy has also been playing a more and more important role in GC treatment. ATTRACTION-2 study revealed that patients with unresectable or recurrent GC treated with anti-PD-1 monoclonal antibodies (mAbs) showed an objective response rate (ORR) of 11.2%(14). Due to the extraordinary result brought by anti-PD-1 mAbs, this measure was incorporated into the third-line treatment for advanced GC in the Japanese guideline. CheckMate-032 study demonstrated that Ipilimumab (anti-CTLA-4 mAbs) plus nivolumab group (anti-PD-1 mAbs) showed a higher objective response rate than nivolumab alone group(15). Although immunotherapy is a promising solution for GC patients, the response rate still limited and novel biomarkers are urgently needed to identify the suitable subgroup of patients.

Tumor mutation burden (TMB) is defined as the non-synonymous somatic mutation number per megabase in cancer cells(16, 17). Several retrospective
and prospective studies demonstrated that TMB could be a promising predictive biomarker for immunotherapy especially for immune checkpoint inhibitors efficacy. Researchers found that high frequency of non-synonymous mutation was associated with higher response rate in both melanoma and non-small cell lung cancer patients treated with ICIs. A pan-cancer analysis showed that TMB was indeed correlated with ICIs treatment response rate. Ten different cancers treated with ICIs were incorporated into the KEYNOTE-158 study and the study result revealed that high TMB was associated with improved ORR and progression-free survival. A phase 2 trial (NCT02915432) also demonstrated that GC patients with high TMB gained significant longer survival advantage than those with low TMB. Therefore, it's worth understanding the TMB status of GC and its relevance with immune cells infiltration.

With the development of bioinformatics, many resources on TMB and immune microenvironment status were available on multiple databases such as The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) database. However, few researches investigate the relationship between them. Therefore, this study was performed to evaluate the prognostic value of TMB and its association with immune cells infiltration in GC patients.

Methods
Transcriptome and somatic mutation data acquisition.

We obtained transcriptome and somatic mutation data from Genomic Data Commons Data Portal of TCGA database (https://portal.gdc.cancer.gov/). Transcriptome profiles of all gastric cancer samples and relative adjacent gastric mucosa samples were downloaded in HTSeq-FPKM format. Somatic mutation data were downloaded in “Masked Somatic Mutation” and processed by VarScan software. The “Maftools” R package(22) was applied to visualize the mutation genes and classification and type of the mutation. The clinical characteristics of GC patients, which including age, gender, AJCC-TNM stage, pathologic stage, tumor grade and living status, were also downloaded from TCGA database.

TMB scores calculation and prognostic analysis

TMB was defined as the total count of somatic mutation of genes which including base substitutions, insertions and deletions. In this research, TMB scores was defined as total number of somatic mutation variants/length of exons. We calculated the TMB scores (mutation frequency) by perl scripts basing on JAVA8 platform. The TMB-high and TMB-low group was defined by median TMB scores. The TMB scores and clinical characteristics of each GC patients were merged by R software. We used Kaplan-Meier analysis to measure the length of survival time and P-value was calculated through log-rank test. The correlation between TMB level and clinical characteristics was analyzed by Wilcoxon rank-sum test.
Identification of differentially expressed genes and pathway enrichment analysis

GC patients were divided by TMB-high and TMB-low group according to the measures as we previously described. Differentially expressed genes (DEGs) were identified by “limma” package and false discovery rate was set as 0.05. Heatmap of DEGs was created by “pheatmap” package. The "org.Hs.eg.db" package was utilized to annotate the DEGs. The Gene ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis were performed by “clusterProfiler”, “enrichplot”, “ggplot2” and both filters of P-value and q-value were set as 0.05. Gene Set Enrichment Analysis (GSEA) was performed by the software downloaded from its official website (https://www.gsea-msigdb.org/gsea) and “c2.cp.kegg.v6.2.symbols.gmt gene sets” was selected as gene set database.

CIBERSORT algorithm

CIBERSORT is an analytical algorithm developed to detect the abundances of cell types in a mixed cell population, using gene expression data(23). Firstly, we prepared the data with “limma” R package. Then we used CIBERSORT algorithm to analyze the immune cell composition in GC patients and visualization was performed by barplot. The violin plot was utilized to visualize the distribution of immune cell and Wilcoxon rank-sum test was used to
evaluate the immune cells infiltration between different TMB group.

**Identification of differentially expressed immune-related genes**

We downloaded immune-related gene list from immport database (https://www.immport.org/shared/genelists) and altogether 2498 genes were obtained. Intersection of DEGs and immune genes was visualized by “VennDiagram” package.

**Establishment of TMB prognostic risk score (TMBPRS) of differentially expressed immune-related genes**

We merged differentially expressed immune-related genes with corresponding survival data and univariate Cox regression analysis was performed to find out the prognostic genes. Multivariate Cox regression analysis was performed to identify the independent risk gene. The TMBPRS was calculated with

\[ TMBPRS = \sum (\chi_i \times EXP_i) \]

and \( \chi_i \) was the coefficient derived from the multivariate Cox regression analysis. Gastric cancer patients were divided into high-risk group and low-risk group with threshold of median risk score. Kaplan-Meier analysis was performed to assess the survival status between the two groups. Receiver Operating Characteristic (ROC) curve was generated to evaluate the predictive value of TMBPRS.

**Timer database**
The “SCNA” module of Timer database (https://cistrome.shinyapps.io/timer/) was designed to compare different immune cells infiltration with different copy number variation (CNV) of a given gene. We used this module to detect the immune cells infiltration with different CNV of the TMB-related immune genes. Box plots were drawn to visualize the distribution of immune cell subset with different CNV and two-sided Wilcoxon rank-sum test was used to calculate the P-value between normal and each mutation group. We also utilized “Survival” module to compare the survival status for immune infiltrates with Kaplan-Meier plots. P-value was calculated through log-rank test.

**Statistical analysis**

The normalization of data and differential analysis was performed by “limma” R package. Cox regression analysis and Kaplan-Meier analysis was performed by “survival” R package. Wilcoxon rank-sum test is a nonparametric test and being used to detect the difference between two groups. All statistical analysis was carried out in R software (Version 3.6.3). P-value <0.05 was considered as statistically significant.

**Results**

**Overview of the mutation status of GC patients**

We obtained the somatic mutation data of GC patients from TCGA and chose the data processed by VarScan software. The “Maftools” R package was
utilized to visualize the landscape of mutation data of GC. According to variant classification, missense mutation, frame shift deletion and nonsense mutation were the first three mutations (Figure 1A). Single nucleotide polymorphism was the most common mutation type, followed by deletion and insertion (Figure 1B). Among the single nucleotide variants (SNV) class, C>T was the most common mutation (Figure 1C). We also countered the number of mutations in each sample and the summary of mutation was visualized in box plot (Figure 1D, E). Top 10 mutated genes in GC were also demonstrated in percentage form, including TTN (48%), MUC16 (31%), TP53 (44%), LRP1B (24%), ARID1A (25%), SYNE1 (22%), FAT4 (19%), CSMD3 (18%), FLG (19%) and PCLO (17%). Mutation of each gene in different samples was showed in waterfall plot (Figure 1G). Besides, genes mutated in more than 30 samples were showed by Genecloud plot (Figure S1). The correlation of mutated genes was shown in Figure 2 and deep green squares indicated co-occurrence while brown squares indicated mutually exclusive.

Assessment of TMB level and prognostic analysis

We calculated the TMB score of each GC samples by perl script. All GC samples were divided into TMB-high and TMB-low group according to median TMB score. Kaplan-Meier analysis was performed to evaluate the survival status between different group. We found that high TMB score was correlated with better survival outcome (Figure 3A). We matched TMB status with
clinicopathological characteristics (Table 1) of GC patients and found that GC patients with age >65y had higher TMB score. Besides, female patients and patients with T1-2 and N0 had higher TMB score than the others (Figure 3B, C, E, F). There was no difference between TMB score and tumor grade and AJCC-M stage (Figure 3D, G).

Comparison of DEGs between TMB-high and TMB-low group and pathway analysis

As we previously described, GC patients were divided into two groups. We compared the DEGs by using "limma" package with |Fold Change| >1 and 816 DEGs were harvested. DEGs between two groups were visualized in heat map (Figure 4A). Go and KEGG analysis were also performed and these DEGs in TMB-high group were mainly involved in neuroactive ligand-receptor interaction, cAMP signaling pathway, calcium signaling pathway (Figure 4B, C and Table 2). GSEA analysis indicated that high TMB level was correlated with splicesome, RNA degradation, cell cycle and base excision repair (Figure 4D). In addition, low TMB level was associated with arachidonic acid metabolism, calcium signaling pathway, neuroactive ligand receptor interaction and vascular smooth muscle contraction (Figure S2).

Immune cell infiltration in TMB-high and TMB-low GC patients

As we have separated two groups of GC patients according to TMB level, we
wanted to investigate the immune cells infiltration between the two groups. By
using "CIBERSORT" R package, we compared 22 immune cells in TMB-high
and TMB-low group. The fraction of 22 immune cells in each GC patients were
shown in Figure 5A and different color represented different immune cell type.
Furthermore, the violin plot was utilized to visualize the immune cell proportion.
Wilcoxon rank-sum test revealed that the infiltration of activated CD4$^+$ memory
T cells, follicular helper T cells, resting NK cells, M0 and M1 macrophages and
neutrophils in TMB-high group were higher compared than that in TMB-low
group (Figure 5B). The absolute abundance of each immune cell type in each
patient was shown in Table 6. In order to further investigate the prognostic role
of immune cells, we constructed a Cox regression model in GC samples and
the formula was demonstrated as follow: Surv (STAD) ~ B cell + CD8$^+$ T cell +
CD4$^+$ T cell + Macrophage + Neutrophil + Dendritic. The result showed that
macrophage infiltration was the only risk factor for GC patients (HR=293.055,
P<0.001 Table 3). Kaplan-Meier analysis was also performed and the result
showed that high macrophage was correlated with inferior survival outcome of
GC patients (Figure 5C).

Identification of immune-related DEGs and TMBPRS establishment
We downloaded immune-related genes from immport database and
“VennDiagram” package was utilized to screen out 96 immune-related genes
(Figure 6A). Univariate Cox regression analysis was performed and further identified 12 prognostic genes (Table 4). TMBPRS was constructed basing on multivariate Cox regression analysis and model was demonstrated as follow:

\[
PRS = (0.001763 \times APOD + 0.033231 \times FGF7 + 0.107249 \times AMHR2 + 0.067987 \times NPR3) \quad \text{(Table 5)}.
\]

And then we calculated the TMBPRS of each GC patients and patients were divided into high-risk and low-risk group with the cutoff value of median. Kaplan-Meier analysis was performed and the result showed that GC patients with high risk had worse survival outcome (Figure 6B). The ROC curve of 1-year overall survival (OS) prediction was drawn with AUC=0.642 (Figure 6C).

**Association between CNV of TMB-related immune genes and immune cell infiltrate.**

As we previously described, we used “VennDiagram” package to identify the intersection between DEGs and immune-related genes and 96 differentially expressed immune-related genes were harvested. Further univariate analysis was applied to identify genes associated with prognosis. At last, we identified 4 hub immune genes (APOD, FGF7, AMHR2, NPR3) that were correlated with TMB. We then further investigated the association between mutants of these hub immune genes and immune cell infiltrate. The “SCNA” module of Timer database was used to analyze the association and B cell, CD8+ T cell, CD4+ T cell, macrophage, neutrophil and dendritic cell were incorporated into the
analyze (Figure 7) Besides, all 4 hub immune genes were also analyzed by Kaplan-Meier method in TCGA and K-M plotter database (Figure S3). The methylation status of the four hub immune genes were also assessed in Figure S4.

**Discussion**

Immunotherapy has brought a revolutionary advance in the field of oncology and immune checkpoint inhibitors played a pivotal role in it. The monoclonal antibody which targets PD-1 and CTLA-4 are the most extraordinary examples of cancer immunotherapy. Human PD-1 is expressed on the surface of T cells and binds to the PD-L1/PD-L2 that are present on antigen-presenting cells (APCs). The PD-1/PD-L1 axis was found negatively regulate T cell activation and its immunosuppression effect is mainly through inhibitory signaling pathway in effect T cells and T\(_{\text{reg}}\) cells(24). Since pembrolizumab and nivolumab were approved by FDA in 2014, they have changed the way of cancer therapy. A phase 3 clinical trial demonstrated that pembrolizumab plus chemotherapy drugs had prolonged the overall survival of non-small-cell lung cancer patients compared with chemotherapy alone(25). Recent study focuses on melanoma also found that patients treated with nivolumab plus ipilimumab remarkably improved their OS with 52% of them survived more than 5 years(26). Another clinical trial showed that atezolizumab plus nab-paclitaxel improved the progression-free survival of metastatic triple-negative breast
cancer patients (27). Besides, myriad of clinical trials demonstrated the efficacy
of anti-PD1/PD-L1 in many cancer types such as urothelial carcinoma, renal
cell carcinoma, small-cell lung cancer (28-30).

Although spectacular result made with immune checkpoint inhibitors,
complicated microenvironment of different organs makes it difficult to predict
which patient will benefit. Several markers such as PD-1/PD-L1
expression (16), microsatellite instability (31) and CD8+ T cell infiltration (32)
have been developed to recognize appropriate patients but their effect were
limited. Therefore, finding better marker to optimize the therapeutic effects of
ICIs is of vital importance.

TMB, a promising marker for ICIs treatment, has been found to play a vital role
in predicting the response of immunotherapy. Ready et al. found that non-small
cell lung cancer patients with high TMB had better response rate and
prolonged progression-free survival when treated with nivolumab plus
low-dose ipilimumab despite of PD-L1 expression (33). Among 22 colorectal
patients treated with PD-1/PD-L1 inhibitors, all TMB-high patients responded
while six out of nine TMB-low patients progressed (34). Besides, TMB also
been demonstrated its effect in various of cancer such as breast cancer,
melanoma, urothelial carcinoma and so on (19, 35, 36). Our study showed that
GC patients with higher TMB had better survival outcome and this finding was
in accordance with other cancer research. In addition, we outlined the TMB-related characteristics of GC patients and observed that TMB-high was correlated with younger age, female, T1-T2 and N0 in GC cases.

In the current study, we calculated the tumor mutation burden score of each GC patients by perl. GC patients then were divided into TMB-high and TMB-low group. By comparing the DEGs between TMB-high and TMB-low group, we identified 816 differently expressed genes. GO and KEGG pathway analysis indicated that these DEGs were mainly involved in neuroactive ligand-receptor interaction, cAMP signaling pathway, calcium signaling pathway and so on. Further uni- and multivariate Cox analysis indicated that AMHR2, APOD, FGF7 and NPR3 were the hub immune genes and correlated with the prognosis of GC patients. We also found that mutant of these genes was correlated with the immune infiltrates. Immune cells infiltration such as B cell, CD8+ T cell, CD4+ T cell, macrophage, neutrophil and dendritic cell were inhibited by the mutation of these genes. To be specific, Arm-level deletion of AMHR2 and FGF7 were associated with reduced infiltration of immune cells. However, Arm-level gain of APOD and NPR3 were associated with reduced infiltration of immune cells.

APOD is an encoding gene which encodes a component of high-density lipoprotein. Researchers found that high expression of APOD was correlated
with worse survival outcome of breast cancer patients (37). Another group also reported that APOD was highly expressed in prostate cancer and high grade prostatic intraepithelial neoplasia compared with adjacent normal tissue (38). FGF7 belongs to fibroblast growth factor (FGF) family and possess mitogenic and cell survival activities. Zhu et al. reported that FGF7 could promote breast cancer progression through AKT signaling pathway (39). In gastric cancer, several studies indicated that FGF7 might play a role in gastric cancer cell proliferation and metastasis (40, 41). The product of gene NPR3 encodes one of the natriuretic peptide receptors and responsible of clearing natriuretic peptides. Previous study demonstrated that high expression of NPR3 was correlated with poor prognosis of colorectal patients (42).

It is widely recognized that immune cells infiltration status had prognostic value in multiple cancer. We compared 22 immune cells between TMB-high and TMB-low group and found that CD4+ memory T cells, follicular helper T cells, resting NK cells, M0 and M1 macrophages and neutrophils were differently infiltrated in the two groups. In order to further investigate whether this difference in the two groups would affect the survival outcome of GC patients, we performed the Cox regression analysis. The result demonstrated that high macrophage infiltration was associated with worse survival outcome of GC patients. Similar conclusion was drawn by Su et al. that high density of macrophage predicted a poor survival outcome of GC patients (43). Several
studies investigated the interaction of macrophage and gastric cancer cell and found that macrophage might play a role in promoting gastric cancer cell proliferation, metastasis, angiogenesis, chemoresistance and immune invasion (44-47).

Finally, a prognostic algorithm (TMBPRS) was constructed according to the Cox regression analysis and patients with high TMBPRS had worse survival outcomes. However, the AUC curve of this algorithm was only 0.642 and therefore large data research was needed to improve the predictive effect.

However, there were some limitations in this study: (a) lack of basic experiment such as immunohistochemistry to identify the correlation between four hub immune genes and immune cells infiltration. (b) large clinical samples are needed to validate the prognostic effect of TMBPRS.

Conclusions

Higher tumor mutation burden was correlated with better survival outcome of GC patients. High macrophage infiltration predicted worse prognosis of GC patients.

Data Availability Statement
The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

**Competing Interests**

The authors declare that there are no competing interests associated with the manuscript.

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**Author contribution**

(I) Conception and design: Jie Yu, SiJia Liang, JinLong Yu

(II) Administrative support: JinLong Yu

(III) Collection and assembly of data: Jie Yu, QianYun Zhang, MengChuan Wang

(IV) Data analysis and interpretation: Jie Yu, QianYun Zhang, MengChuan Wang, SiJia Liang, HongYun Huang, Lang Xie

(V) Manuscript writing: All authors

(VI) Final approval of manuscript: All authors
**Abbreviations**

1. TMB, tumor mutation burden; GC, gastric cancer; DEGs, differentially expressed genes; TMBPRS, TMB prognostic risk score; ICIs, immune checkpoint inhibitors; mAbs, monoclonal antibodies; ORR, objective response rate; TCGA, The Cancer Genome Atlas; GEO, Gene Expression Omnibus; GO, Gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; GSEA, Gene Set Enrichment Analysis; ROC, Receiver Operating Characteristic; OS, overall survival.

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Figure legends

Figure 1: Summary of mutation landscape of GC samples from TCGA database.

(A, B, C) Mutation types basing on different categories, where missense mutation was the most frequent component and SNP was the most common mutation type and C > T was the most common type of SNV. (D, E) Tumor mutation burden of each GC samples and its classification and the median variants number was 89. (F). Top 10 mutated genes in GC samples and TTN, MUC16 and TP53 was the TOP 3 mutated genes. (G) Waterfall plot of mutation profiles of each gene in each sample. The legend at the bottom described the mutation types. The plot above the legends showed the mutation burden of each sample. GC, gastric cancer.

Figure 2: Pair of mutually exclusive or co-occurring mutated genes. Pair-wise Fisher’s Exact test was used to detect the statistic difference.

Figure 3: Prognostic value of TMB and its association with clinical characteristics.

(A) Higher TMB level was correlated with better survival outcome of GC patients, P=0.017. (B, C, E, F) Higher TMB was associated with lower age, female, lower AJCC-T stage and lower AJCC-N stage. (D, G) No statistic difference were observed between TMB and tumor grade and AJCC-M stage. TMB, tumor mutation burden
Figure 4: Comparison of DEGs between TMB-high and TMB-low group and pathway analysis.

(A). Top 40 DEGs between TMB-high and TMB-low group were shown in heatmap. (B, C) GO and KEGG analysis of DEGs between TMB-high and TMB-low group. (D) GSEA analysis indicated that high TMB was correlated with spliceosome, RNA degradation, cell cycle and base excision repair. DEGs, differentially expressed genes; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; TMB, tumor mutation burden.

Figure 5: Immune cells infiltration between TMB-high and TMB-low group and survival analysis of immune cells.

(A) 22 types of immune cells infiltration status in each GC sample. (B) The comparison of immune cells infiltration between TMB-high and TMB-low group. (C) Kaplan-Meier analysis of different immune cells and high macrophage infiltration was correlated with worse survival outcome of GC patients. GC, gastric cancer; TMB, tumor mutation burden.

Figure 6: Identification of hub immune genes and construction of TMBPRS.

(A) Identification of differentially expressed immune-related genes through Venn plot. (B) Assessment of TMBPRS in GC patients and patients with high TMBPRS had worse survival outcome (P=0.00032). (C) ROC plot of TMBPRS with AUC=0.642. AUC, area under curve; GC, gastric cancer; ROC, receiver
operating characteristic; TMBPRS, tumor mutation burden prognostic risk score.

Figure 7: Correlation between mutants of 4 hub immune genes and immune cells infiltration

(A) Correlation between mutants of AMHR2 and immune cells infiltration. Arm-level deletion of AMHR2 was correlated with reduced infiltration level of B cell, CD8+ T cell, CD4+ T cell, macrophage, neutrophil and dendritic cell.

(B) Correlation between mutants of APOD and immune cells infiltration. Arm-level gain of APOD was correlated with reduced infiltration level of B cell, CD8+ T cell, CD4+ T cell, macrophage, neutrophil and dendritic cell.

(C) Correlation between mutants of FGF7 and immune cells infiltration. Arm-level deletion of FGF7 was correlated with reduced infiltration level of B cell, CD8+ T cell, CD4+ T cell, macrophage, neutrophil and dendritic cell.

(D) Correlation between mutants of NPR3 and immune cells infiltration. Arm-level gain of NPR3 was correlated with reduced infiltration level of B cell, CD8+ T cell, CD4+ T cell, macrophage, neutrophil and dendritic cell.

Figure S1: Genecloud plot of mutated genes in GC. GC, gastric cancer.

The size of each gene in the genecloud plot was positively correlated with mutation frequency in GC samples.
Figure S2: GSEA analysis of TMB-low samples.

GSEA analysis indicated that low TMB was correlated with (A) arachidonic acid metabolism, (B) calcium signaling pathway, (C) neuroactive ligand receptor interaction and (D) vascular smooth muscle contraction. TMB, tumor mutation burden.

Figure S3: Kaplan-Meier analysis of 4 hub immune genes in TCGA database and K-M plotter database.

Kaplan-Meier analysis of 4 hub immune genes in TCGA database (A) AMHR2, (B) APOD, (C) FGF7 and (D) NPR3. Kaplan-Meier analysis of hub immune genes in K-M plotter database (E) AMHR2, (F) APOD, (G) FGF7 and (H) NPR3

Figure S4: Methylation status of 4 hub immune genes and its association with gene expression and clinical characteristics. Different colors with specific annotations at the bottom meant the various characteristics of each GC patients.

(A) The expression of AMHR2 was negatively correlated with methylation around the promoter region.

(B) The expression of APOD was negatively correlated with methylation around the promoter region.

(C) No correlation was observed between FGF7 expression and methylation
around the promoter region.

(D) The expression of NPR3 was positively correlated with H. pylori infection.

Tables

Table 1: Clinical characteristics of TCGA gastric cancer patients.

Table 2: KEGG analysis of the DEGs in TMB-high group. DEGs, differentially expressed genes; TMB, tumor mutation burden.

Table 3: Multivariate Cox regression analysis of immune infiltration cells in gastric cancer.

Table 4: Univariate Cox regression analysis of immune-related DEGs.

Table 5: Multivariate Cox regression analysis of immune-related DEGs.

Table 6: Absolute abundance of each immune cell type in GC patients.
Altered in 387 (89.38\%) of 433 samples.
A heat map showing the correlation between different genes. The colors represent the significance of the correlation:

- **P < 0.001**
- **P < 0.05**

The genes are listed along the top and left side of the map. The significance levels are indicated by the color intensity and the presence of a star symbol. The map includes the following genes:

- PIK3CA [63]
- CSMD1 [63]
- SPTA1 [64]
- ZFHX4 [65]
- RYR2 [66]
- HMCN1 [67]
- OBSCN [68]
- FAT3 [68]
- KMT2D [69]
- DNAH5 [70]
- PCLO [72]
- CSMD3 [79]
- FAT4 [82]
- FLG [84]
- SYNE1 [94]
- LRP1B [105]
- ARID1A [109]
- MUC16 [133]
- TP53 [189]
- TTN [208]

The color gradient indicates the number of co-occurrences or mutual exclusivity:

- **>3 (Co-occurrence)**
- **>3 (Mutually exclusive)**

The exact P-values are not provided in the diagram.
**A**

Venn diagram showing sets of samples with the following counts:
- 173 samples in set A
- 96 samples in set B
- 530 samples in set C
- 75 samples in set A and B
- 96 samples in set A and C
- 1 sample in sets A, B, and C

**B**

Survival analysis graph comparing high-risk and low-risk strata. The graph shows survival probabilities over time with the following statistics:
- P-value: 0.00032
- Hazard Ratio (HR): 1.82

**C**

ROC curve with an AUC of 0.642.
| Variables | TCGA cohort (N=443) |
|-----------|---------------------|
| Status    |                     |
| Alive     | 272 (61.4)          |
| Dead      | 171 (38.6)          |
| Age       | 66±10.76            |
| Gender    |                     |
| Female    | 158 (35.6)          |
| Male      | 285 (64.4)          |
| AJCC-T    |                     |
| T1        | 23 (5.2)            |
| T2        | 93 (21.0)           |
| T3        | 198 (44.7)          |
| T4        | 119 (26.9)          |
| TX        | 10 (2.2)            |
| AJCC-N    |                     |
| N0        | 132 (29.8)          |
| N1        | 119 (26.9)          |
| N2        | 85 (19.2)           |
| N3        | 88 (19.9)           |
| NX        | 17 (3.8)            |
| Unknown   | 2 (0.4)             |
| AJCC-M    |                     |
| M0        | 391 (88.3)          |
| M1        | 30 (6.8)            |
| MX        | 22 (4.9)            |
| Pathologic stage |       |
| I&II      | 192 (43.3)          |
| III&IV    | 224 (50.6)          |
| Unknown   | 27 (6.1)            |
| Tumor grade |                 |
| G1-G2     | 171 (38.6)          |
| G3        | 263 (59.4)          |
| GX        | 9 (2.0)             |
| Description                              | BgRatio | pvalue     | p.adjust  | qvalue      |
|------------------------------------------|---------|------------|-----------|-------------|
| Neuroactive ligand-receptor interaction  | 340/8040| 2.58E-11   | 6.64E-09  | 0.0000001   |
| Vascular smooth muscle contraction       | 132/8040| 4.90E-08   | 6.30E-06  | 0.0000537   |
| cAMP signaling pathway                   | 216/8040| 2.44E-07   | 2.09E-05  | 0.0001779   |
| Calcium signaling pathway                | 193/8040| 4.46E-07   | 2.86E-05  | 0.0002440   |
| Dilated cardiomyopathy (DCM)             | 96/8040 | 1.62E-06   | 8.33E-05  | 0.00007096  |
| Arrhythmogenic right ventricular cardiomyopathy | 77/8040 | 3.33E-06   | 0.00014   | 0.00011966  |
| Hypertrophic cardiomyopathy (HCM)        | 90/8040 | 3.83E-06   | 0.00014   | 0.00011966  |
| Pancreatic secretion                      | 102/8040| 1.70E-05   | 0.000546  | 0.00046522  |
| Cell adhesion molecules (CAMs)           | 148/8040| 2.40E-05   | 0.000685  | 0.00058390  |
| Insulin secretion                        | 86/8040 | 5.79E-05   | 0.001487  | 0.00126717  |
| cGMP-PKG signaling pathway               | 167/8040| 0.000112   | 0.002621  | 0.00223331  |
| Protein digestion and absorption         | 95/8040 | 0.000155   | 0.00331   | 0.00281991  |
| Renin secretion                          | 69/8040 | 0.000811   | 0.014904  | 0.01269720  |
| Fat digestion and absorption             | 43/8040 | 0.000812   | 0.014904  | 0.01269720  |
| Focal adhesion                           | 201/8040| 0.000996   | 0.016124  | 0.01373677  |
| Adrenergic signaling in cardiomyocytes   | 149/8040| 0.001004   | 0.016124  | 0.01373677  |
| Drug metabolism - cytochrome P450        | 72/8040 | 0.001108   | 0.016744  | 0.01426520  |
| Aldosterone-regulated sodium reabsorption| 37/8040 | 0.001959   | 0.027971  | 0.02382945  |
| Cortisol synthesis and secretion         | 65/8040 | 0.002295   | 0.031038  | 0.02644201  |
| Aldosterone synthesis and secretion      | 98/8040 | 0.002842   | 0.036521  | 0.03111326  |
| Chemical carcinogenesis                   | 83/8040 | 0.003022   | 0.036981  | 0.03150577  |
| ECM-receptor interaction                 | 88/8040 | 0.004487   | 0.052421  | 0.04465959  |
| Bile secretion                           | 90/8040 | 0.005209   | 0.058203  | 0.04958528  |
| Cell types     | coef  | HR   | 95%CI_l | 95%CI_u | p.value | sig |
|---------------|-------|------|---------|---------|---------|-----|
| B_cell        | 3.262 | 26.096 | 0.419   | 1625.426| 0.122   | -   |
| CD8_Tcell     | -2.040| 0.130 | 0.009   | 1.966   | 0.141   | -   |
| CD4_Tcell     | -3.825| 0.022 | 0.000   | 1.763   | 0.088   | -   |
| Marcophag     | 5.680 | 293.055 | 15.915  | 5396.255| 0.000 ***| *** |
| Neutrophil    | -0.629| 0.533 | 0.003   | 88.445  | 0.809   | -   |
| Dendritic     | 1.506 | 4.510 | 0.401   | 50.764  | 0.223   | -   |
| Gene    | HR  | HR.95L | HR.95H | CoxPvalue |
|---------|-----|--------|--------|-----------|
| SLC22A17 | 1.067292 | 1.023803 | 1.112629 | 0.002153 |
| APOD    | 1.002423 | 1.001157 | 1.003692 | 0.000175 |
| CMA1    | 1.155618 | 1.043777 | 1.279444 | 0.005354 |
| FGF7    | 1.048351 | 1.016115 | 1.081609 | 0.003044 |
| OGN     | 1.006824 | 1.001391 | 1.012288 | 0.013767 |
| AMHR2   | 1.109999 | 1.038009 | 1.186982 | 0.002286 |
| GHR     | 1.215142 | 1.071306 | 1.378290 | 0.002433 |
| GLP2R   | 1.412913 | 1.092291 | 1.827648 | 0.008483 |
| NPR3    | 1.073467 | 1.009318 | 1.141694 | 0.024136 |
| PTGER3  | 1.149958 | 1.018448 | 1.298451 | 0.024135 |
| PTGFR   | 1.198121 | 1.043102 | 1.376179 | 0.010561 |
| PTH1R   | 1.440015 | 1.056238 | 1.963235 | 0.021113 |
| id   | coef    | HR   | HR.95L | HR.95H | coxPvalue |
|------|---------|------|--------|--------|-----------|
| APOD | 0.001763| 1.001765 | 1.000301 | 1.00323 | 0.018081  |
| FGF7 | 0.033231| 1.03379 | 0.998769 | 1.070039 | 0.058773  |
| AMHR2| 0.107249| 1.113211 | 1.037874 | 1.194017 | 0.002702  |
| NPR3 | 0.067987| 1.070352 | 0.998354 | 1.147541 | 0.055671  |
| Mixture                  | B cells naïve | B cells mem | Plasma cell | T cells CD8 | T cells CD4 | T cells CD4 |
|-------------------------|---------------|-------------|-------------|-------------|-------------|-------------|
| TCGA-BR-8381-01A-11R-2402-13 | 0.038522      | 0           | 0.044155    | 0.287094    | 0           | 0.125966    |
| TCGA-BR-A46-01A-11R-A251-31  | 0.221858      | 0           | 0.327528    | 0.090268    | 0           | 0.152557    |
| TCGA-VQ-A8PE-01A-11R-A414-31  | 0.128187      | 0           | 0           | 0.118479    | 0           | 0.256744    |
| TCGA-D7-8572-01A-11R-2343-13  | 0.094482      | 0           | 0.006857    | 0.064831    | 0           | 0.115045    |
| TCGA-BR-8080-01A-11R-2343-13  | 0.138085      | 0           | 0.00095     | 0.107448    | 0           | 0.349662    |
| TCGA-BR-4280-01A-01R-1131-13  | 0.084881      | 0           | 0.102067    | 0.112611    | 0           | 0.18027     |
| TCGA-MX-A666-01A-11R-A31P-31  | 0.398376      | 0.073307    | 0.049096    | 0.049401    | 0           | 0.133646    |
| TCGA-CG-5726-01A-11R-1602-13  | 0.097946      | 0           | 0.011768    | 0.12462     | 0           | 0.228917    |
| TCGA-CD-A489-01A-11R-A24K-31  | 0.224342      | 0           | 0           | 0.153019    | 0           | 0.245688    |
| TCGA-RD-A8N9-01A-11R-A251-31  | 0.107784      | 0           | 0.070759    | 0.10726     | 0           | 0.201487    |
| TCGA-BR-8485-01A-11R-2402-13  | 0.077086      | 0           | 0.20364     | 0.236876    | 0           | 0.277928    |
| TCGA-IN-7808-01A-11R-2203-13  | 0.189727      | 0.13278     | 0.054427    | 0.164136    | 0           | 0.129216    |
| TCGA-HF-7131-01A-11R-2055-13  | 0.182054      | 0           | 0.067165    | 0.066441    | 0           | 0.320888    |
| TCGA-HU-A4H0-01A-11R-A251-31  | 0.056642      | 0           | 0.013913    | 0.183148    | 0           | 0.243055    |
| TCGA-IN-8663-01A-11R-2402-13  | 0.030208      | 0           | 0.022146    | 0.031952    | 0           | 0.119326    |
| TCGA-VQ-A91Y-01A-11R-A414-31 | 0.050725 | 0 | 0.009986 | 0.115375 | 0 | 0.282776 |
|-------------------------------|---------|---|---------|---------|---|---------|
| TCGA-CD-5801-01A-11R-1602-13  | 0.117121 | 0 | 0.03807 | 0.39133 | 0 | 0.182844 |
| TCGA-HU-A4GJ-01A-11R-A251-31  | 0.226764 | 0.08181 | 0.110483 | 0.116423 | 0 | 0.213441 |
| TCGA-BR-7715-01A-11R-2055-13  | 0.067281 | 0 | 0.006201 | 0.053518 | 0 | 0.115993 |
| TCGA-D7-A747-01A-22R-A33Y-31  | 0.246803 | 0.017405 | 0 | 0.114213 | 0 | 0.213441 |
| TCGA-VQ-AA6F-01A-31R-A414-31  | 0.194493 | 0 | 0.091413 | 0.088637 | 0 | 0.231649 |
| TCGA-CD-5813-01A-11R-1602-13  | 0.110124 | 0 | 0.048618 | 0.156127 | 0 | 0.13701 |
| TCGA-BR-4363-01A-01R-1157-13  | 0.043463 | 0 | 0.014833 | 0.086831 | 0 | 0.26201 |
| TCGA-BR-8366-01A-11R-2343-13  | 0.000156 | 0.00538 | 0.022365 | 0.215232 | 0 | 0.182844 |
| TCGA-BR-8690-01A-11R-2402-13  | 0.029565 | 0.040183 | 0.005946 | 0.063157 | 0 | 0.213441 |
| TCGA-VQ-A91U-01A-11R-A414-31  | 0.077518 | 0.004643 | 0.105514 | 0.185144 | 0 | 0.231649 |
| TCGA-BR-6452-01A-12R-1802-13  | 0.063977 | 0 | 0.032561 | 0.030331 | 0 | 0.13701 |
| TCGA-RD-A7C1-01A-11R-A32D-31  | 0.146354 | 0 | 0.010288 | 0.079904 | 0 | 0.326928 |
| TCGA-BR-6564-01A-12R-1884-13  | 0.10656 | 0 | 0.015866 | 0.197908 | 0 | 0.23416 |
| TCGA-HU-A4HB-01A-12R-A251-31  | 0.17028 | 0 | 0.015866 | 0.197908 | 0 | 0.13701 |
| TCGA-VQ-A925-01A-11R-A39E-31  | 0.097061 | 0 | 0.043966 | 0.045397 | 0 | 0.13701 |
| TCGA-VQ-A8PC-01A-11R-A39E-31  | 0.003462 | 0.105375 | 0.002702 | 0.074268 | 0 | 0.182844 |
| TCGA-BR-4201-01A-01R-1131-13  | 0.052002 | 0 | 0.001681 | 0.178822 | 0 | 0.23416 |
| TCGA-VQ-A94R-01A-11R-A31P-31  | 0.076724 | 0 | 0.04637 | 0.091643 | 0 | 0.326928 |
| TCGA-VQ-A91E-01A-11R-A36D-31  | 0.077518 | 0 | 0.004643 | 0.105514 | 0 | 0.13701 |
| TCGA-D7-A6EV-01A-11R-A33Y-31  | 0.097061 | 0 | 0.043966 | 0.045397 | 0 | 0.13701 |
| TCGA-HU-A4G2-01A-11R-A251-31  | 0.003462 | 0 | 0.002702 | 0.074268 | 0 | 0.13701 |
| TCGA-VQ-A94R-01A-11R-A31P-31  | 0.076724 | 0 | 0.04637 | 0.091643 | 0 | 0.13701 |
| ID                  | Value 1 | Value 2 | Value 3 | Value 4 | Value 5 | Value 6 |
|---------------------|---------|---------|---------|---------|---------|---------|
| TCGA-HU-A4H8-01A-11R-A251-31 | 0       | 0.016034 | 0.002933 | 0.102498 | 0       | 0.271308 |
| TCGA-BR-8284-01A-11R-2343-13 | 0.061207 | 0       | 0.004548 | 0.292353 | 0       | 0.255488 |
| TCGA-RD-A8MV-01A-11R-A36D-31 | 0.070026 | 0.010121 | 0.011359 | 0.114919 | 0       | 0.192318 |
| TCGA-HU-A4G3-01A-11R-A24K-31 | 0.041769 | 0.019507 | 0       | 0.075419 | 0       | 0.361848 |
| TCGA-HU-A4GU-01A-11R-A251-31 | 0.070416 | 0       | 0.006364 | 0.067634 | 0       | 0.311823 |
| TCGA-HU-A4G8-01A-11R-A251-31 | 0.065449 | 0.075801 | 0       | 0.077318 | 0       | 0.231358 |
| TCGA-IN-A6RJ-01A-21R-A33Y-31 | 0.028795 | 0.009376 | 0.03407  | 0.078668 | 0       | 0.237302 |
| TCGA-CG-5719-01A-11R-1602-13 | 0.035809 | 0       | 0.084801 | 0.036998 | 0       | 0.215205 |
| TCGA-BR-8286-01A-12R-2343-13 | 0.015696 | 0       | 0       | 0.150474 | 0       | 0.156609 |
| TCGA-CG-5716-01A-21R-1802-13 | 0.027995 | 0.103058 | 0.219496 | 0.080052 | 0       | 0.245870 |
| TCGA-D7-6526-01A-11R-1884-13 | 0.14478  | 0       | 0       | 0.138915 | 0       | 0.239377 |
| TCGA-D7-A6EZ-01A-11R-A31P-31 | 0.024219 | 0       | 0.006156 | 0.161082 | 0       | 0.081278 |
| TCGA-D7-8578-01A-21R-2343-13 | 0.032461 | 0       | 0.002197 | 0.261544 | 0       | 0.255691 |
| TCGA-CG-4305-01A-01R-1157-13 | 0.089286 | 0       | 0.003263 | 0.110442 | 0       | 0.169881 |
| TCGA-D7-A4YX-01A-11R-A251-31 | 0.032461 | 0       | 0.002197 | 0.261544 | 0       | 0.255691 |
| TCGA-D7-6815-01A-11R-1884-13 | 0.068239 | 0       | 0.016957 | 0.064274 | 0       | 0.104397 |
| TCGA-EQ-8122-01A-11R-2343-13 | 0.06732  | 0       | 0       | 0.031583 | 0       | 0.099693 |
| TCGA-HU-A4GQ-01A-11R-A36D-31 | 0.029468 | 0       | 0.002862 | 0.105896 | 0       | 0.096091 |
| TCGA-BR-4256-01A-01R-1131-13 | 0.079346 | 0       | 0.001245 | 0.058401 | 0       | 0.166647 |
| TCGA-CG-4466-01A-11R-1157-13 | 0.086833 | 0       | 0       | 0.058401 | 0       | 0.307343 |
| TCGA-CG-4466-01A-11R-1157-13 | 0.029468 | 0       | 0.002862 | 0.105896 | 0       | 0.307343 |
| TCGA-KB-A93J-01A-11R-A39E-31 | 0.069817 | 0       | 0.072559 | 0.075862 | 0       | 0.135446 |
| TCGA-VQ-A92D-01A-11R-A414-31 | 0.035636 | 0       | 0.001706 | 0.041067 | 0       | 0.197105 |
| TCGA-VQ-A91V-01A-11R-A414-31 | 0.073184 | 0       | 0.02537  | 0.109367 | 0       | 0.264605 |
| TCGA-CD-8534-01A-11R-2343-13 | 0.164334 | 0       | 0.005018 | 0.074892 | 0       | 0.301570 |
| TCGA-VQ-A8PU-01A-12R-A414-31 | 0.060546 | 0       | 0.037491 | 0.015347 | 0       | 0.197105 |
| TCGA-VQ-A94T-01A-11R-A414-31 | 0.048808 | 0       | 0.00351  | 0.190537 | 0       | 0.151091 |
| TCGA-CD-8531-01A-11R-2343-13 | 0.032461 | 0       | 0.002197 | 0.261544 | 0       | 0.255691 |
| TCGA-VQ-AA69-01A-11R-A414-31 | 0.132967 | 0       | 0.070216 | 0.072762 | 0       | 0.297744 |
| TCGA-VQ-AA6D-01A-11R-A414-31 | 0.129234 | 0       | 0.031797 | 0.051585 | 0       | 0.418408 |
| TCGA-B7-A5TN-01A-21R-A31P-31 | 0.079346 | 0       | 0.001245 | 0.153021 | 0       | 0.253846 |
| TCGA-B7-A5TI-01A-11R-A31P-31 | 0.073184 | 0       | 0.02537  | 0.109367 | 0       | 0.264605 |
| TCGA-F1-6875-01A-11R-2055-13 | 0       | 0       | 0.013054 | 0.001025 | 0       | 0.272451 |
| TCGA-FP-A8CX-01A-11R-A36D-31 | 0.028158 | 0.000923 | 0.073193 | 0.120996 | 0       | 0.162358 |
| TCGA-FP-A8CX-01A-11R-A36D-31 | 0.028158 | 0.000923 | 0.073193 | 0.120996 | 0       | 0.272451 |
| TCGA-FP-A8CX-01A-11R-A36D-31 | 0.028158 | 0.000923 | 0.073193 | 0.120996 | 0       | 0.162358 |
| TCGA-FP-A8CX-01A-11R-A36D-31 | 0.028158 | 0.000923 | 0.073193 | 0.120996 | 0       | 0.272451 |
| TCGA-BR-4371-01A-01R-1157-13 | 0 | 0 | 0.00432 | 0.01609 | 0.395666 |
| TCGA-BR-4253-01A-01R-1131-13 | 0.02284 | 0 | 0.002215 | 0.203075 | 0 | 0.31276 |
| TCGA-F1-A448-01A-11R-A24K-31 | 0.140523 | 0 | 0.072247 | 0.038801 | 0 | 0.163972 |
| TCGA-CG-5734-01A-11R-1602-13 | 0.059159 | 0 | 0.099418 | 0.07842 | 0.377997 |
| TCGA-VQ-A8DT-01A-11R-A36D-31 | 0.140523 | 0 | 0.072247 | 0.038801 | 0 | 0.163972 |
| TCGA-CG-5725-01A-11R-1602-13 | 0.099904 | 0 | 0.009871 | 0.213837 | 0.090973 |
| TCGA-HU-8238-01A-11R-2343-13 | 0.100006 | 0 | 0.004266 | 0.07059 | 0.163972 |
| TCGA-VQ-A94U-01A-12R-A414-31 | 0.066678 | 0 | 0.022388 | 0.142156 | 0.377997 |
| TCGA-VQ-A8DZ-01A-11R-A36D-31 | 0.055824 | 0 | 0.003743 | 0.111868 | 0.233526 |
| TCGA-F1-A72C-01A-21R-A33Y-31 | 0.07213 | 0 | 0.049515 | 0.183018 | 0.204415 |
| TCGA-VQ-A922-01A-11R-A414-31 | 0.174401 | 0 | 0.014268 | 0.048166 | 0.314741 |
| TCGA-VQ-A91Z-01A-11R-A414-31 | 0.080732 | 0 | 0.01611 | 0.028554 | 0.178572 |
| TCGA-BR-8382-01A-11R-2402-13 | 0.059871 | 0 | 0.009871 | 0.213837 | 0.090973 |
| TCGA-VQ-A8P2-01A-11R-A36D-31 | 0.137995 | 0 | 0.023228 | 0.14483 | 0.354847 |
| TCGA-D7-6822-01A-11R-1884-13 | 0.035972 | 0 | 0.001372 | 0.122034 | 0.245038 |
| TCGA-RD-A8NB-01A-12R-A39E-31 | 0.136114 | 0 | 0.054165 | 0.23418 | 0.174365 |
| TCGA-BR-8592-01A-11R-2402-13 | 0.142227 | 0 | 0.026869 | 0.33402 | 0.10417 |
| TCGA-BR-8678-01A-11R-2402-13 | 0.059871 | 0 | 0.009871 | 0.213837 | 0.090973 |
| TCGA-CG-4441-01A-01R-1802-13 | 0.116585 | 0 | 0.010337 | 0.091966 | 0.189114 |
| TCGA-HU-A4GH-01A-11R-A24K-31 | 0.217923 | 0 | 0.014398 | 0.091966 | 0.189114 |
| TCGA-VQ-A8PO-01A-11R-A414-31 | 0.072292 | 0.009583 | 0 | 0.205171 | 0.182856 |
| TCGA-BR-A4CR-01A-11R-A24K-31 | 0.148498 | 0 | 0.013769 | 0.279928 |
| TCGA-IN-AB1V-01A-21R-A414-31 | 0.07845 | 0.143168 | 0.024837 | 0.156197 | 0.145174 |
| TCGA-CG-4437-01A-01R-1802-13 | 0.078002 | 0 | 0.011358 | 0.243338 | 0.042901 |
| TCGA-CG-4304-01A-01R-1157-13 | 0.085122 | 0 | 0.171854 | 0.02323 | 0.193194 |
| TCGA-CG-5723-01A-11R-1602-13 | 0.000114 | 0.007373 | 0.011352 | 0.220602 | 0.120957 |
| TCGA-CG-5725-01A-11R-1602-13 | 0.099904 | 0 | 0.099418 | 0.07842 | 0.377997 |

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| TCGA-BR-8686-01A-11R-2402-13 | 0.107804 0 0 0.261899 0 0.224366 |
|-----------------------------|-----------------------------------|
| TCGA-BR-6802-01A-11R-1884-13 | 0.058107 0 0.01486 0.24651 0 0.003019 |
| TCGA-BR-A477-01A-31R-A251-31 | 0.070331 0 0.008517 0.326459 0 0.199962 |
| TCGA-BR-4191-01A-02R-1131-13 | 0.031632 0 0.001414 0.079163 0 0.211414 |
| TCGA-BR-4366-01A-01R-1157-13 | 0.001305 0.014521 0 0.07395 0 0.166052 |
| TCGA-HU-8244-01A-11R-2343-13 | 0.070331 0 0.008517 0.326459 0 0.199962 |
| TCGA-BR-7722-01A-31R-2203-13 | 0.051294 0 0.003012 0.066146 0 0.242636 |
| TCGA-FP-8631-01A-11R-2402-13 | 0.078728 0 0.029107 0.014063 0 0.243437 |
| TCGA-BR-4369-01A-01R-1157-13 | 0.107904 0 0.113545 0.047623 0 0.296929 |
| TCGA-VQ-A923-01A-11R-A414-31 | 0.079295 0 0.003012 0.223577 0 0.192437 |
| TCGA-BR-7851-01A-11R-2203-13 | 0.075028 0 0.001602 0.111824 0 0.203228 |
| TCGA-D7-8574-01A-13R-2343-13 | 0.004347 0.346691 0.014222 0.140656 0 0.251197 |
| TCGA-BR-8683-01A-11R-2402-13 | 0.085998 0 0.006431 0.247456 0 0.125034 |
| TCGA-BR-7723-01A-11R-2055-13 | 0.024984 0 0.038911 0.135957 0 0.16611 |
| TCGA-VQ-A91Q-01A-12R-A414-31 | 0.104365 0.123672 0.006431 0.247456 0 0.125034 |
| TCGA-BR-6453-01A-11R-1884-13 | 0.045353 0 0.00886 0.222052 0 0.229973 |
| TCGA-FP-7998-01A-11R-2203-13 | 0.081489 0 0.034122 0.24451 0 0.114752 |
| TCGA-BR-8365-01A-11R-2343-13 | 0.089258 0 0.02202 0.078634 0 0.203101 |
| TCGA-BR-7717-01A-11R-2055-13 | 0.18107 0 0.000688 0.183748 0 0.205267 |
| TCGA-D7-6521-01A-11R-1802-13 | 0.188471 0 0.140544 0 0.13732 |
| TCGA-VQ-A8E3-01A-11R-2343-13 | 0.091394 0 0.007247 0.065907 0 0.199817 |
TCGA-D7-A4YU-01A-21R-A251-31 0.06047 0.014116 0.006033 0.105286 0 0.1 50774
TCGA-HU-A4HD-01A-11R-A251-31 0.057989 0 0.005477 0.080701 0 0.194293
TCGA-BR-4361-01A-01R-1157-13 0.031307 0 0.003489 0.115497 0 0.202526
TCGA-VQ-A927-01A-12R-A414-31 0.016604 0 0.140112 0.049888 0 0.448966
TCGA-BR-8384-01A-21R-2402-13 0.093941 0 0.213771 0 0.254664
TCGA-VQ-A91X-01A-12R-A414-31 0.123124 0 0.069987 0.101094 0 0.14935
TCGA-D7-6522-01A-11R-1802-13 0.076611 0.058646 0.032543 0.196248 0 0.090267
TCGA-HU-A4HD-01A-11R-2402-13 0.031364 0.063084 0.025715 0.143811 0 0.23088
TCGA-D7-A748-01A-12R-A32D-31 0.055062 0 0.009056 0.018818 0 0.191472
TCGA-VQ-A8PJ-01A-11R-A414-31 0.130617 0 0.057534 0.038897 0 0.328604
TCGA-D7-6524-01A-11R-1802-13 0.024658 0 0 0.068648 0 0.163578
TCGA-BR-6566-01A-11R-1802-13 0.011059 0.012058 0.004037 0.111868 0 0.235471
TCGA-FP-A4BF-01A-12R-A36D-31 0.029368 0 0.05419 0.175734 0 0.203878
TCGA-CG-4438-01A-01R-1157-13 0.04088 0 0.00662 0.135926 0 0.229394
TCGA-BR-6456-01A-11R-1802-13 0.048898 0 0 0.116734 0 0.178489
TCGA-CG-4460-01A-01R-1157-13 0.107755 0 0.082959 0.047988 0 0.192841
TCGA-VQ-AA68-01A-11R-A414-31 0.21821 0 0.029653 0.141789 0 0.151915
TCGA-D7-8575-01A-11R-2343-13 0.153849 0 0.03063 0.002315 0 0.132655
TCGA-BR-4367-01A-01R-1157-13 0.01377 0 0.027883 0.107282 0 0.19595
TCGA-VQ-A8P5-01A-11R-A39E-31 0.116524 0 0.05926 0.092748 0 0.162189
TCGA-VQ-A94O-01A-11R-A414-31 0.071949 0 0.015138 0.043028 0 0.218969
TCGA-VQ-A8E2-01A-11R-A36D-31 0.151244 0 0.034525 0.093395 0 0.120849
TCGA-RD-A8N0-01A-12R-A36D-31 0.02822 0.204422 0.087543 0.181747 0 0.200838
TCGA-BR-7901-01A-11R-2203-13 0.048689 0 0.005493 0.10081 0 0.182497
TCGA-BR-8081-01A-11R-1884-13 0.015845 0 0 0.056953 0 0.263709
TCGA-RD-A8N5-01A-12R-A36D-31 0.041137 0 0.003032 0 0.177003
TCGA-BR-6455-01A-11R-1802-13 0.088518 0 0.00206 0.332797 0 0.05843
TCGA-BR-4294-01A-01R-1131-13 0.065275 0 0.111817 0.123118 0 0.187523
TCGA-BR-8081-01A-11R-2343-13 0.064654 0 0.19543 0.103164 0 0.149628
TCGA-D7-6519-01A-11R-1802-13 0.022885 0 0 0.227833 0 0.159353
TCGA-VQ-A91S-01A-11R-A414-31 0.03229 0 0 0.279689 0 0.154145
TCGA-BR-A4J8-01A-11R-A251-31 0.05365 0.017071 0 0.069485 0 0.280998
TCGA-CD-8528-01A-11R-2343-13 0.015105 0 0 0.04828 0 0.19986
TCGA-SW-A7EB-01A-11R-A354-31 0.218704 0 0.054473 0.123122 0 0.20864
TCGA-VQ-A91N-01A-11R-A414-31 0.158176 0 0.155037 0.089962 0 0.246492
TCGA-CG-4442-01A-01R-1157-13 0.021156 0 0 0.066959 0 0.196322
TCGA-HF-A5NB-01A-11R-A31P-31 0.017104 0 0 0.203266 0 0.263591
TCGA-FP-8210-01A-11R-2343-13 0.133771 0.087448 0.024962 0.174013 0 0.154838
TCGA-VQ-A8PM-01A-21R-A414-31 0.128844 0 0.251652 0.058087 0 0.229833
TCGA-VQ-A928-01A-11R-A414-31 0.054403 0 0.005851 0.02739 0 0.272157
TCGA-HU-A4GY-01A-21R-A24K-31 0.08738 0.144761 0 0.102916 0 0.244719
TCGA-HU-A4H4-01A-21R-A251-31 0.12821 0 0.092653 0.080395 0 0.154145
TCGA-CD-8503-01A-11R-1602-13 0.064561 0 0.005237 0.245539 0 0.225107
T cells CD4 T cells follic T cells regu T cells gam NK cells res NK cells act Monocytes Macrophag Macrophag Macrophag

0.10008 0.06847 0.072017 0 0.005915 0 0.00271 0.071537 0.064206 0.097981
0 0.02592 0.011736 0 0 0.051067 0.010136 0 0.00787 0.044705
0.061745 0.039479 0.027432 0 0.035869 0 0.154705 0.05474 0.061412
0.027734 0.018873 0.019546 0 0.030089 0 0.397876 0.045172 0.100081
0 0.01409 0.019993 0.0243 0 0.01604 0 0.71815 0.069562 0.109038
0.144465 0.033836 0.003925 0 0.0455 0 0.00271 0.047271 0.090308
0 0.045606 0.066576 0 0 0.031369 0 0.75467 0 0.30385
0.052593 0 0.18982 0 0.038744 0 0 0.165618 0.055856 0.131562
0 0.023075 0.022739 0 0 0.051047 0.004586 0.017709 0.035399 0.19312
0.038767 0.064836 0.098201 0 0 0.006505 0.000732 0.070403 0.052008 0.108717
0.065357 0.023663 0.040651 0 0.024897 0.000843 0.100163 0.03037 4 0.053916
0.001614 0.031924 0.10139 0 0 0.043855 0 0.45481 0.03915 0.047321
0.017527 0 0.067505 0 0.02803 0 0.012131 0.072889 0.026601 0.05309
0.150524 0.058436 0.002355 0 7.71E-05 0 0.001929 0.001087 0.14072 0.110192
0.026644 0.04337 0.053848 0 0 0.022176 0 0.461229 0.026748 0.149824
0.017401 0.030187 0 0 0.040784 0 0.100163 0.03037 4 0.053916
0.047306 0.065841 0.010686 0 0 0.062063 6.51E-06 0.152799 0.100987 0.126802
0.118092 0 0.109936 0 0 0.003177 0.080274 0.098315 0.146485
0.026592 0 0.07074 0 0 0.008287 0.00765 0.06495 0.028846 0.06606
0.158103 0.046546 0.006534 0 0 0.020011 0.014257 0 0.74393 0.11297 0.08897
0.076644 0 0.002655 0 0 0.061801 0 0 0.42053 0.079337 0.042585
0.003009 0 0.035468 0 0 0.023504 0.006887 0.004955 0.011062
0.096156 0.012441 0.015047 0 0 0.00691 0 0.00277 0.063796 0.034742 0.065158
0 0.078168 0.029869 0 0 0.013006 0 0 0.08463 0.050149
0.017933 0.068004 0 0 0 0.061323 0.01446 0.000242 0.034226 0.063928
0.066629 0.070244 0.032741 0 0 0.01183 0 0.127019 0.102241 0.208496
0.032948 0.014667 0.0775 0 0 0.041881 0.004511 0.058335 0.116632 0.07704
0.10335 0.02027 0 0 0.038554 0 0 0.133287 0.063896 0.133526
0.081243 0.00304 0.012015 0 0 0.076815 0 0.22686 0.00426 0.073824
0.082273 0 0.024615 0 0 0.031394 0 0 0.296459 0 0.035274
0.151536 0 0.04086 0 0 0.040342 0 0 0.084406 0.09732 0.084467
0.057819 0.046827 0.04499 0 0 0.031474 0.002734 0.136446 0.050847 0.103489
0.008504 0.045234 0.02456 0 0 0 0.364571 0.129913 0.071749
0.101243 0.045261 0.074652 0.001406 0 0 0 0.059832 0.039513 0.071643
0.171087 0.023196 0.008694 0 0 0.044451 0.012 0.128123 0.075522 0.136537
0.001833 0.000483 0.03108 0 0 0.020414 0.028887 0.184017 0.046863 0.136042
0.016283 0.02331 0 0.013349 0.001344 0 0 0.062881 0.049158 0.302687
0.004137 0.08739 0.008565 0 0 0.058645 0 0.020297 0.172335 0 0.458429
0.093063 0.024209 0.08189 0 0 0.069022 0 0 0.204928 0.088992 0.128881
0.094795 0.009992 0.05529 0 0 0.032543 0.010513 0.041044 0.040358 0.036168
0.05174 0 0.050557 0 0 0.020045 0 0.02214 0.050881 0.049386 0.03056
0.090587 0 0 0 0.048514 0 0 0.074047 0.03955 0.080615
0 0.036336 0.008208 0 0 0.022812 0.002189 0.140414 0.072714 0.174549
0.014315 0 0.027253 0 0 0.005649 0 0 0.069683 0.01759 0.08962
| Dendritic ce | Mast cells | Mast cells | Eosinophils | Neutrophils |
|-------------|------------|------------|-------------|-------------|
| 0.013416    | 0.001931   | 0          | 0.006       | 0           |
| 0.016966    | 0.001326   | 0.038064   | 0           | 0           |
| 0.000546    | 0.013692   | 0          | 0.046968    | 0           |
| 0           | 0          | 0.077805   | 0           | 0.001608    |
| 0.031319    | 0          | 0.069568   | 0           | 0           |
| 0.003611    | 0          | 0.006065   | 0.00438     | 0.01581     |
| 0.014982    | 0.031789   | 0          | 0           | 0           |
| 0.027634    | 0          | 0.032095   | 0.014026    | 0           |
| 0.034421    | 0          | 0.068664   | 0           | 0           |
| 0.021891    | 0          | 0.050651   | 0           | 0           |
| 0.012883    | 0          | 0.019869   | 0           | 0           |
| 0           | 0          | 0.012751   | 0.001593    | 0.00487     |
| 0.000559    | 0.017442   | 0.002905   | 0.020005    | 0.044769    |
| 0.005006    | 0          | 0.032916   | 0           | 0           |
| 0           | 0          | 0          | 0.002323    | 0           |
| 0.025555    | 0          | 0.057709   | 0.006287    | 0           |
| 0.077784    | 0.005131   | 0.028894   | 0           | 0           |
| 0.023435    | 0          | 0.053238   | 0           | 0           |
| 0.008937    | 0          | 0.043216   | 0           | 0.001947    |
| 0.020494    | 0.021497   | 0.02989    | 0           | 0.014191    |
| 0           | 0.016681   | 0.030966   | 0           | 0.001478    |
| 0.038073    | 0          | 0.026881   | 0           | 0           |
| 0           | 0          | 0          | 0.033974    | 0           |
| 0.010898    | 0.14273    | 0          | 0           | 0.002323    |
| 0.026346    | 0.003487   | 0.0244     | 0           | 0           |
| 0.114547    | 0          | 0.019548   | 0           | 0.008337    |
| 0.008058    | 0.037335   | 0.065854   | 0           | 0           |
| 0.002766    | 0          | 0.011335   | 0.008403    | 0.071379    |
| 0.065462    | 0          | 0.121688   | 0           | 0           |
| 0.016118    | 0          | 0.014658   | 0           | 0.01145     |
| 0           | 0.08133    | 0.132403   | 0           | 0.023908    |
| 0.025344    | 0.048688   | 0          | 0.243698    | 0.054412    |
| 0           | 0.010176   | 0          | 0.08684     | 0.016036    |
| 0.071284    | 0          | 0.021885   | 0           | 0           |
| 0           | 0          | 0.031019   | 0           | 0           |
| 0.002631    | 0          | 0.005334   | 0           | 0           |
| 0.021643    | 0          | 0.065133   | 0           | 0.007796    |
| 0.035911    | 0.017779   | 0.164059   | 0           | 0           |
| 0.052727    | 0.037103   | 0          | 0.097566    | 0.086531    |
| 0           | 0          | 0          | 0.063362    | 0           |
| 0.002039    | 0          | 0.055799   | 0           | 0           |
| 0.019635    | 0          | 0.046585   | 0           | 0           |
| 0.017736    | 0.023553   | 0.01766    | 0.005442    | 0.000659    |
| 0.04088     | 0          | 0.009861   | 0           | 0.017464    |
| 0.011383    | 0.009313   | 0          | 0.008456    | 0           |
|      |      |      |      |      |      |
|------|------|------|------|------|------|
| 0.004582 | 0.033866 | 0.033338 | 0  | 0  | 0  |
| 0.013253  | 0  | 0.036338 | 0  | 0  | 0  |
| 0.002554  | 0.021752 | 0.031776 | 0  | 0  | 0.053349 |
| 0  | 0.01637 | 0.114737 | 0.029209 | 0  | 0.033975 |
| 0  | 0  | 0  | 0.018989 | 0  | 0.012719 |
| 0  | 0.008799 | 0.019097 | 0  | 0  | 0  |
| 0.073185 | 0.054821 | 0.105567 | 0  | 0  | 0.003224 |
| 0.002578  | 0  | 0  | 0.031439 | 0  | 0.011551 |
| 0.049199  | 0.013005 | 0.051573 | 0  | 0.000117 |
| 0  | 0.05955 | 0.036127 | 0  | 0  | 0.006782 |
| 0  | 0.072113 | 0  | 0.079306 | 0  | 0.242045 |
| 0.015049  | 0.013445 | 0.053068 | 0  | 0  | 0.006129 |
| 0  | 0  | 0  | 0.101003 | 0  | 0.011785 |
| 0.034501  | 0.016896 | 0.040787 | 0.011946 | 0.001807 | 0.021455 |
| 0.038542  | 0  | 0  | 0.103426 | 0.02321 | 0.059492 |
| 0  | 0.024787 | 0  | 0.051983 | 0  | 0.001242 |
| 0.002077  | 0  | 0  | 0.076142 | 0  | 0  |
| 0  | 0.128122 | 0  | 0.144039 | 0  | 0.020908 |
| 0  | 0  | 0  | 0.019608 | 0  | 0.009629 |
| 0.007623  | 0  | 0.034213 | 0  | 0  | 0.002736 |
| 0.024428  | 0.011888 | 0.049449 | 0  | 0  | 0  |
| 0.008367  | 0  | 0.025572 | 0  | 0  | 0  |
| 0  | 0.076425 | 0.015566 | 0  | 0  | 0.046292 |
| 0  | 0.026909 | 0  | 0.104291 | 0.015729 | 0.013677 |
| 0.008379  | 0.017456 | 0.053602 | 0  | 0  | 0  |
| 0  | 0.161313 | 0  | 0.004369 | 0  | 0  |
| 0.01759   | 0  | 0.015598 | 0  | 0  | 0.001536 |
| 0.006378  | 0  | 0.023237 | 0.00224 | 0.025401 | 0.005732 |
| 0.018948  | 0  | 0.047326 | 0  | 0  | 0.007468 |
| 0.002166  | 0.051258 | 0.079703 | 0  | 0  | 0  |
| 0.05228   | 0  | 0.039082 | 0.044275 | 0.003851 | 0.064012 |
| 0.023954  | 0  | 0.03551  | 0  | 0  | 0  |
| 0  | 0.034202 | 0  | 0.109047 | 0  | 0  |
| 0.013778  | 0.024901 | 0.044892 | 0  | 0  | 0.004666 |
| 0.015954  | 0  | 0.008747 | 0  | 0.021384 | 0.010197 |
| 0.030821  | 0.002559 | 0.045741 | 0  | 0  | 0  |
| 0  | 0  | 0  | 0.149839 | 0.006236 | 0  |
| 0.025779  | 0  | 0.040298 | 0  | 0  | 0  |
| 0.123985  | 0  | 0.073649 | 0  | 0  | 0  |
| 0.003176  | 0  | 0.004418 | 0.021677 | 0.05738 |
| 0  | 0  | 0.040235 | 0  | 0  | 0  |
| 0.033874  | 0.011698 | 0.072618 | 0  | 0  | 0.04745 |
| 0.004248  | 0.00678 | 0.042224 | 0  | 0  | 0  |
| 0.045675  | 0  | 0.054085 | 0  | 0  | 0  |
| 0  | 0.023003 | 0.098289 | 0.02829 | 0  | 0.076492 |
| 0  | 0.031183 | 0.038702 | 0  | 0  | 0.016611 |
| 0  | 0.0106  | 0  | 0.032442 | 0  | 0.023209 |
|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 0.035919 | 0.005619 | 0.035923 | 0 | 0 | 0.001931 |
| 0.006599 | 0.005654 | 0.023031 | 0 | 0.002048 | 0.010065 |
| 0 | 0.006277 | 0 | 0.180015 | 0 | 0.04749 |
| 0.006888 | 0.0055 | 0 | 0.029558 | 0.003186 | 0.024185 |
| 0.001695 | 0.021561 | 0.070523 | 0 | 0 | 0.021096 |
| 0.015867 | 0.054572 | 0 | 0.062249 | 0 | 0 |
| 0 | 0 | 0 | 0.04653 | 0.067994 | 0 |
| 0 | 0 | 0 | 0.050213 | 0 | 0.004496 |
| 0 | 0 | 0 | 0.039993 | 0.153679 | 0.015766 |
| 0 | 0 | 0 | 0.046511 | 0 |
| 0.058212 | 0 | 0.102491 | 0 | 0 | 0.00266 |
| 0.01994 | 0.009285 | 0.031339 | 0.015031 | 0 | 0.076158 |
| 0 | 0.008465 | 0.007214 | 0.002742 | 0 | 0.001219 |
| 0 | 0 | 0 | 0.044152 | 0 |
| 0 | 0 | 0 | 0.046511 | 0 |
| 0.020776 | 0.004238 | 0 | 0.007588 | 0 | 0.041665 |
| 0 | 0.085607 | 0 | 0.180093 | 0 | 0.108389 |
| 0 | 0 | 0 | 0.046395 | 0.02181 |
| 0 | 0 | 0 | 0.079572 | 0 |
| 0 | 0 | 0 | 0.059633 | 0.000471 | 0 |
| 0.016739 | 0 | 0.000301 | 0 | 0 | 0.114647 |
| 0.024017 | 0.007621 | 0.006863 | 0.006259 | 0 | 0 |
| 0.01578 | 0 | 0.052789 | 0 | 0 |
| 0 | 0.021622 | 0.036339 | 0 | 0.001657 | 0 |
| 0 | 0 | 0.037792 | 0 |
| 0.076724 | 0 | 0.05187 | 0 | 0 |
| 0.00093 | 0.012646 | 0 | 0.088154 | 0 | 0.056726 |
| 0.012348 | 0.000798 | 0 | 0.009413 | 0.001671 | 0 |
| 0.020986 | 0.081562 | 0 | 0.067183 | 0.015174 | 0.01542 |
| 0.017656 | 0.01433 | 0.02064 | 0 | 0 | 0.002153 |
| 0.024628 | 0.005593 | 0.058461 | 0 | 0 | 0.015182 |
| 0.002891 | 0 | 0.08812 | 0 | 0 |
| 0 | 0 | 0 | 0.039688 | 0.00035 | 0.00167 |
| 0.018595 | 0.043931 | 0 | 0.097799 | 0.001916 | 0.026916 |
| 0 | 0.034137 | 0 | 0.08632 | 0 | 0.025158 |
| 0.004025 | 0.006833 | 0.087148 | 0 | 0 | 0.062369 |
| 0.011169 | 0.0011 | 0.004442 | 0.001844 | 0.012329 | 0.097051 |
| 0 | 0 | 0 | 0.008848 | 0.000537 | 0 |
| 0 | 0 | 0 | 0.056756 | 0.01505 | 0.008193 |
| 0.017154 | 0.002349 | 0.018924 | 0.000977 | 0 | 0.049198 |
| 0.051188 | 0 | 0.004722 | 0 | 0.000713 | 0 |
| 0.046107 | 0.004705 | 0.008575 | 0 | 0 | 0.000834 |
| 0 | 0.049439 | 0 | 0.133256 | 0 | 0.02525 |
| 0.031382 | 0.016587 | 0.047326 | 0 | 0 | 0.003616 |
| 0.024487 | 0 | 0.021753 | 0 | 0 | 0 |
| 0 | 0 | 0.004777 | 0 | 0 | 0.020463 |
|    |    |    |    |    |    |
|----|----|----|----|----|----|
| 0.006828 | 0.046007 | 0.0 | 0.0 | 0.008843 |
| 0.01065 | 0.017366 | 0.0 | 0.0 |    |
| 0.105828 | 0.018533 | 0.062506 | 0.007212 |
| 0.006177 | 0.001945 | 0.0 |    |
| 0.02334 | 0.032453 | 0.008578 |
| 0.064755 | 0.125447 | 0.0 |    |
| 0.160284 | 0.071118 | 0.007614 |
| 0.128051 | 0.060601 | 0.01842 |    |
| 0.019724 | 0.018405 | 0.0 |    |
| 0.011313 | 0.023827 | 0.000546 |
| 0.021512 | 0.027725 | 0.005811 |
| 0.044383 | 0.062932 | 0.00828 |
| 0.01093 | 0.013472 | 0.107826 | 0.030681 |
| 0.015058 | 0.020313 | 0.007864 |
| 0.00374 | 0.01023 | 0.0 |    |
| 0.11232 | 0.019601 | 0.097605 | 0.0 |
| 0.05506 | 0.025485 | 0.04826 | 0.001737 |
| 0.00458 | 0.00756 | 0.009035 |
| 0.006122 | 0.05072 | 0.0 |    |
| 0.0 | 0.010885 | 0.005868 |    |
| 0.01389 | 0.008773 | 0.0213 | 0.0 |
| 0.057227 | 0.02978 | 0.023832 |    |
| 0.029387 | 0.031389 | 0.048464 | 0.003842 |
| 0.0 | 0.072371 | 0.0 |
| 0.001857 | 0.044163 | 0.008823 |
| 0.003063 | 0.0 |    |
| 0 | 0.010408 | 0.024667 | 0.078121 |
| 0.000129 | 0.010282 | 0.0 |    |
| 0.02368 | 0.044353 | 0.0 |    |
| 0.064479 | 0.001599 | 0.040821 | 0.02144 |
| 0.03549 | 0.041967 | 0.002215 |
| 0.018057 | 0.008878 | 0.068124 |    |
| 0 | 0.036183 | 0.0 |
| 0.001204 | 0.0172062 | 0.032791 | 0.039152 |
| 0.012256 | 0.103939 | 0.000606 | 0.033594 |
| 0.003515 | 0.092079 | 0.0 |    |
| 0.034827 | 0.007265 | 0.024066 | 0.001836 |
| 0 | 0.087153 | 0.003642 |
| 0.026587 | 0.00615 | 0.021221 |
| 0.00435 | 0.117622 | 0.07164 |    |
| 0 | 0.039054 | 0.038223 | 0.001975 |
| 0 | 0.031092 | 0.042977 | 0.034455 |
| 0.036181 | 0.00993 | 0.059286 | 0.003767 |
| 0.040239 | 0.019547 | 0.054984 | 0.010023 |
| 0 | 0.0105 | 0.037064 | 0.037312 |
| 0.013121 | 0.008722 | 0.096763 | 0.012581 |
|    |      |      |      |      |      |
|----|------|------|------|------|------|
| 0  | 0.002343 | 0.033137 | 0   | 0   | 0   |
| 0.021964 | 0   | 0.064798 | 0.001632 | 0   | 0.00604 |
| 0.019318 | 0   | 0.004473 | 0.004466 | 0.017612 | 0.001784 |
| 0.004748 | 0.018418 | 0.033095 | 0   | 0.017563 | 0.015676 |
| 0.05948  | 0.016561 | 0.076595 | 0   | 0   | 0   |
| 0.02652  | 0   | 0.055897 | 0   | 0   | 0   |
| 0.026133 | 0.049961 | 0   | 0   | 0.006149 |
| 0.035401 | 0.002172 | 0.028169 | 0   | 0   | 0   |
| 0.059878 | 0   | 0.029242 | 0   | 0.01403 | 0.005221 |
| 0.068028 | 0.004194 | 0.041068 | 0   | 0   | 0.068451 |
| 0.026886 | 0.01355  | 0.031906 | 0   | 0   | 0   |
| 0.05076  | 0.048517 | 0   | 0.232858 | 0    | 0.165198 |
| 0.008459 | 0   | 0.115728 | 0   | 0   | 0   |
| 0.02016  | 0   | 0.00806  | 0   | 0   | 0.004567 |
| 0.004965 | 0.000656 | 0.012637 | 0   | 0.001082 | 0   |
| 0.01075  | 0   | 0.037915 | 0   | 0   | 0   |
| 0.004406 | 0   | 0.091152 | 0   | 0   | 0   |
| 0.014106 | 0   | 0.090377 | 0.03564 | 0.022185 |
| 0.007344 | 0.017126 | 0.067632 | 0   | 0   | 0   |
| 0   | 0.006896 | 0   | 0.047162 | 0.003263 |
| 0.000257 | 0   | 0.008642 | 0.007022 | 0.023573 | 0.032907 |
| 0.013106 | 0   | 0.13463  | 0.00116  | 0   | 0   |
| 0   | 0   | 0.003215 | 0   | 0   | 0   |
| 0.006102 | 0.009647 | 0.045235 | 0   | 0   | 0   |
| 0.026353 | 0.000275 | 0.104411 | 0.010474 | 0   | 0.010224 |
| 0.004536 | 0   | 0.026314 | 0   | 0.006144 |
| 0.011259 | 0   | 0.027953 | 0   | 0   | 0   |
| 0.023905 | 0   | 0.123782 | 0   | 0.135437 |
| 0.011509 | 0   | 0.009271 | 0   | 0   | 0   |
| 0.013064 | 0.0043  | 0   | 0.002198 | 0.102272 | 0.041144 |
| 0.008043 | 0.009861 | 0   | 0.01751  | 0   | 0   |
| 0.02305  | 0.001058 | 0.102601 | 0   | 0   | 0   |
| 0.011782 | 0   | 0.008393 | 0   | 0.025159 |
| 0.000882 | 0   | 0.117747 | 0   | 0   | 0   |
| 0.010665 | 0   | 0.003993 | 0   | 0.007467 |
| 0.002177 | 0   | 0.030809 | 0   | 0   | 0   |
| 0.049927 | 0.017177 | 0.029391 | 0   | 0.007026 | 0   |
| 0.000969 | 0   | 0.035205 | 0.004378 | 0.086954 |
| 0.032399 | 0   | 0   | 0.045445 | 0   | 0   |
| 0.053816 | 0.029794 | 0.049031 | 0   | 0.010053 |
| 0.033442 | 0.016619 | 0.041308 | 0   | 0   | 0   |
| 0.015912 | 0   | 0.125743 | 0.000467 | 0.006788 |
| 0.010943 | 0.005667 | 0.019506 | 0   | 0   | 0   |
| 0.054391 | 0.037382 | 0   | 0.016023 |
| 0.054791 | 0.012825 | 0.019558 | 0   | 0   | 0   |
| 0.005142 | 0.005099 | 0 | 0.01945 | 0 | 0 |
| 0 | 0 | 0 | 0.126811 | 0.022935 | 0.129105 |
| 0.017106 | 0.003346 | 0 | 0.003579 | 0 | 0.01229 |
| 0.000438 | 0 | 0.056818 | 0 | 0 | 0 |
| 0.008871 | 0.01421 | 0 | 0.107274 | 0 | 0.081735 |
| 0.016884 | 0 | 0.07186 | 0 | 0.000828 | 0.035961 |
| 0.01756 | 0.00441 | 0.009772 | 0 | 0.001231 | 0 |
| 0.15557 | 0 | 0 | 0.03088 | 0 | 0 |
| 0 | 0.003966 | 0.056244 | 0.000765 | 0 | 0.019447 |
| 0.007035 | 0 | 0.16265 | 0 | 0.016822 |
| 0 | 0.042357 | 0.059011 | 0 | 0.049884 |
| 0.003442 | 0.02003 | 0.014958 | 0.012968 | 0 | 0 |
| 0 | 0 | 0.188822 | 0 | 0.006779 |
| 0.007393 | 0.005342 | 0.030662 | 0 | 0 | 0 |
| 0.039969 | 0 | 0.091339 | 0 | 0 | 0 |
| 0.017235 | 0 | 0 | 0.056469 | 0.00585 | 0 |
| 0.015466 | 0.008165 | 0.054148 | 0 | 0 | 0.005264 |
| 0.037899 | 0.02067 | 0.11543 | 0 | 0 | 0.00772 |
| 0 | 0 | 0 | 0.068762 | 0.000321 | 0.024163 |
| 0 | 0.037362 | 0 | 0.251787 | 0.016826 | 0.100928 |
| 0 | 0.092651 | 0 | 0.141745 | 0 | 0.034507 |
| 0.007364 | 0.006057 | 0.094652 | 0 | 0.025354 | 0.143599 |
| 0.006873 | 0 | 0.082265 | 0 | 0 | 0 |
| 0.010531 | 0.004307 | 0 | 0.056585 | 0 | 0.084607 |
| 0 | 0.000581 | 0.000329 | 0.004868 | 0 | 0.004908 |
| 0.019584 | 0.012397 | 0.085537 | 0 | 0 | 0 |
| 0.051869 | 0 | 0.015104 | 0 | 0 | 0 |
| 0 | 0 | 0.014465 | 0 | 0 | 0 |
| 0.062189 | 0 | 0.047144 | 0 | 0.001786 | 0 |
| 0.011058 | 0 | 0.02825 | 0 | 0 | 0 |
| 0 | 0.05042 | 0.037089 | 0 | 0 | 0 |
| 0.009171 | 0.023521 | 0.041791 | 0 | 0 | 0 |
| 0.051152 | 0.021192 | 0.021808 | 0.037063 | 0 | 0.001017 |
| 0.01172 | 0 | 0.026247 | 0 | 0 | 0.023915 |
| 0.014306 | 0 | 0 | 0.047243 | 0.030962 | 0.044779 |
| 0 | 0.042051 | 0 | 0.014264 | 0 | 0.022941 |
| 0.002936 | 0.075827 | 0 | 0 | 0.000385 | 0.014812 |
| 0.000549 | 0 | 0.035437 | 0 | 0 | 0 |
| 0 | 0.026043 | 0.013866 | 0.098186 | 0 | 0.05443 |
| 0.01798 | 0 | 0.09199 | 0 | 0.029333 | 0 |
| 0.013243 | 0.010177 | 0.024494 | 0 | 0 | 0 |
| 0.023645 | 0.045297 | 0 | 0.038324 | 0.038329 | 0.236077 |
| 0.025766 | 0.014293 | 0 | 0.09091 | 0.006251 | 0.011321 |
| 0.030782 | 0 | 0.060072 | 0 | 0.029776 | 0.073062 |
| 0 | 0.008078 | 0.015032 | 0 | 0 | 0 |
| 0.087668 | 0.037755 | 0 | 0.03545 | 0.003084 | 0 |
| 0.031084 | 0 | 0.060542 | 0 | 0 | 0 |