# TREM2 is a prognostic biomarker and correlates in immune infiltrates in kidney renal papillary cell carcinoma and liver hepatocellular carcinoma

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# TREM2 is a prognostic biomarker and correlates in immune infiltrates in kidney renal papillary cell carcinoma and liver hepatocellular carcinoma

**Abstract**

Background: TREM2 was identified as a marker for tumor-associated macrophages (TAMs) and monocytes. However, there is limited information concerning the TREM2 mRNA levels correlated with the outcome and tumor-infiltrating lymphocytes in different cancers.

Methods: To explore the expression pattern and prognostic value of TREM2 in pan-cancer, We use multiple databases, including ONCOMINE, PrognoScan, Kaplan-Meier Plotter, GEPIA, and TIMER. we investigated the correlations between TREM1 expression and immune infiltration in cancers, especially kidney renal papillary cell carcinoma (KIRP), and liver hepatocellular carcinoma (LIHC)

Results: According to the results from Oncomine and TIMER datasets, in a general way, TREM2 mRNA expression is higher in the majority of the tumor and is lower in lung cancer, compared with normal adjacent tissues. A high expression level of TREM2 was beneficial to the survival of LIHC patients. Both in KIRP and LIHC, TREM2 expression levels showed significant positive correlations with infiltrating levels of macrophages and dendritic cells. It also correlated with diverse immune marker sets. We can also find that TREM2 expression was modestly associated with CD8+T cells in KIRP. However, it is related to the Treg in LIHC.

Conclusions: TREM2 may be a prognostic marker in the multitudinous tumor. Furthermore, TREM2 may interact with immune infiltration to influence patient survival in cancers like LIHC and KIRP.

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**Introduction**

Papillary renal cell carcinoma (PRCC) accounts for 10-15% of renal clear cell carcinoma, Which is the most common malignancy among both men and women worldwide[1]. The number of people suffering from Papillary renal cell carcinoma each year increases to 6-9000. In renal clear cell carcinoma, immune-related mechanisms play an essential role, and immune-oncology strategies can be seen as a promising path for renal clear cell carcinoma[2]. However, most of the FDA proved therapeutic drugs are for CCRCC[3], Mainly targeted therapy (anti-angiogenesis), plus the old immunotherapy interleukin-2 has been tested on papilloma, but with little success[4, 5]. Moreover, more and more studies have shown that the prognosis and effectiveness of chemotherapy and immunotherapy are impaired by tumor-infiltrating lymphocytes, such as tumor-associated macrophages and tumor-infiltrating neutrophils. There is an urgent need to explain the immune phenotype of tumor-immune interactions in Papillary renal cell carcinoma and develop new immune-related therapeutic targets.

TREM2 is one of the Ig-superfamily members. When TREM2 binds to an adaptor protein DAP12, activation signaling is transmitted. The function and pathological significance of trem2 have been extensively studied in non-cancerous diseases, such as Alzheimer's disease[6, 7]. TREM2 is expressed in microglia cells and various types of tissue-resident cell macrophages[8]. Accumulating evidence suggests that TREM2 plays a vital role in promoting the immune-suppressive microenvironment of cancer tumors. An analysis of

45    gastric cancer samples observed that TREM2 mRNA and protein expression were substantially

46    higher relative to normal gastric tissues. The high expression of Trem2 predicted poor

47    prognosis[9]. TREM2 has been proposed as a target for Glioma[10] and liver cancer[11]

48    because its upregulation is associated with tumor progression. Recently, Katzenelenbogen et

49    al. Give sufficient evidence to illustrate that trem2 is a marker for tumor-associated

50    macrophages (TAMs) and monocytes[12]. It attracted our attention to the tumor inhabitation

51    role and mechanism of Trem2. Whether tumor immune infiltrates and clinical effects are

52    correlated with trem2 levels in Papillary renal cell carcinoma tissues has not been evaluated.

53    Our study comprehensively evaluated the prognostic landscape of TREM2 in databases such

54    as Oncomine, PrognoScan, and Kaplan-Meier plotter. Through the Tumor Immune Estimation

55    Resource (TIMER) and GEPIA, we investigated the association of time with tumor-infiltrating

56    immune cells in various tumor microenvironments. Our findings shed light on the crucial role

57    of Trem2 in Papillary renal cell carcinoma and provide a potential relationship and an

58    underlying mechanism between Papillary renal cell carcinoma and tumor-immune

59    interactions.

60

61    **Materials & Methods**

62    Expression of trem2 in human tumors

63    The expression level of the TREM2 gene in various types of cancers was analyzed in the

64    Oncomine    database(https://www.oncomine.org/resource/login.html)[13].    The    thresholds

65    were set as a P-value of 0.001, fold change of 1.5, and gene ranking of all.

66    Survival analysis

67　The correlation between The mRNA expression of TREM2 and survival in different cancer

68　types of cancers was analyzed by the PrognoScan database

69　(http://dna00.bio.kyutech.ac.jp/PrognoScan/index.html)[14], GEPIA(http://gepia.cancer-

70　pku.cn/)[15], and Kaplan-Meier Plotter(https://kmplot.com/analysis/)[16].PrognoScan looks

71　through a wide range of freely accessible cancer microarray databases for determining

72　relationships between gene expression and patient prognosis, such as overall survival (OS)

73　and disease-free survival (DFS). The threshold was set as a Cox P-value < 0.05. Besides, we

74　downloaded TREM2 RNAseq data and clinical data of GDC TCGA Kidney Papillary Cell

75　Carcinoma (KIRP) from UCSC-XENA(https://xenabrowser.net/datapages/)[17] and integrated

76　the data via EXCEL. We did univariate survival analysis via GraphPad. The survival analysis

77　from PrognoScan was summarized and visualized via forest map was drawn by GraphPad and

78　adobe illustrator.

79　GEPIA, an interactive web server, is usually utilized to analyze the RNA sequencing expression

80　data, including 9,736 tumors and 8,587 normal samples from the TCGA and the GTEx projects.

81　We generate survival curves in each available cancer type (total number=34), including OS

82　and DFS, with the Spearman method determining the correlation coefficient.

83　The Kaplan-Meier plotter can identify the effect of 54000 genes on survival in 21 tumors. We

84　explored the impact of trem2 expression on OS and RFS and calculated Ratios (HRs) with 95%

85　confidence intervals (CI) and log-rank P values.

86　Trem2 expression and immune cell associations in TIMER and GEPIA

87　We determine the relationship between Trem2 expression and immune infiltration via TIMER

88　(https://cistrome.shinyapps.io/timer/)[18] and GEPIA databases. TIMER is a powerful online

89    tool that does a systematic analysis of immune infiltrates across diverse cancer types. a

90    previously published statistical deconvolution method is applied to infer the abundance of

91    tumor-infiltrating immune cells from gene expression profiles. 10,897 samples across 32

92    cancer types from The Cancer Genome Atlas (TCGA) are contained to estimate immune

93    infiltrates quantity. We analyzed the correlation of trem2 expression with infiltrating cells the

94    abundance of immune infiltrates, including B cells, CD4+ T cells, CD8+ T cells, neutrophils,

95    macrophages, and dendritic cells and also determined the relationship of gene expression

96    levels with tumor purity. To identify the potential subtypes of infiltrating immune cells.   We

97    further analyzed the correlation between TREM2 expression and several immune cell markers.

98    These markers are determined by referencing studies previously, respectively, markers of

99    CD8+ T cells, T cells (general), B cells, monocytes, TAMs, M1 macrophages, M2 macrophages,

100   neutrophils, natural killer (NK) cells, dendritic cells (DCs), T-helper 1 (Th1) cells, T-helper 2

101   (Th2) cells, follicular helper T (Tfh) cells, T-helper 17 (Th17) cells, Tregs, and exhausted T

102   cells,  Log2 RSEM was used to be the standard of adjusting the gene expression level.

103   Correlations between trem2 and each immune gene marker were displayed via scatter plots.

104   The plots include Spearman's correlation and the estimated statistical significance. Also, trem2

105   as a gene symbol is for the x-axis, and related marker genes are plotted on the y-axis as gene

106   symbols.

107   Statistical analysis

108   The results from Oncomine datasets are seen with P-values, fold changes, and ranks. As for

109   the survival curves, the log-rank test was the standard method to calculate HR and log-rank

110   P-value in Kaplan-Meier Plotter and GEPIA., while in PrognoScan, HR and Cox P value was

111     calculated by a Univariate Cox regression model. Spearman's correlation was used to

112     calculate the gene expression correlation, if not explicitly stated, P-values < 0.05 is deemed

113     statistically significant.

114

115     **Results**

116     The mRNA expression levels of TREM2

117     Comparing with that in the respective normal groups, TREM2 is highly expressed in bladder

118     cancer, brain and CNS cancer, breast cancer, cervical cancer, colorectal cancer, esophageal

119     cancer, stomach cancer, head and neck cancer, kidney cancer, pancreatic cancer, and prostate

120     cancer. Besides, TREM2 expression is lower in lung cancer compared to normal tissues(Figure

121     1A). We summarized the detailed results of TREM2expression in multiple cancers in

122     Supplementary Table 1.

123     To further evaluate TREM2 expression in human cancers, we used the RNA-seq data of

124     multiple malignancies in TCGA, examining TREM2expression(Figure 1B). TREM2 expression

125     was significantly higher in BLCA(bladder urothelial carcinoma) 、 BRCA(breast invasive

126     carcinoma)、CESC(Cervical squamous cell carcinoma and endocervical adenocarcinoma)、

127     CHOL(Cholangiocarcinoma)、COAD(colon adenocarcinoma)、GBM(Glioblastoma multiforme)、

128     HNSC(head and neck cancer) 、 KICH(kidney chromophobe) 、 KIRC(kidney renal clear cell

129     carcinoma)、KIRP(Kidney renal papillary cell carcinoma)、LIHC(liver hepatocellular carcinoma)、

130     PRAD(prostate adenocarcinoma) 、 STAD(stomach adenocarcinoma) 、 THCA(thyroid

131     carcinoma)、UCEC(uterine corpus endometrial carcinoma). Besides that, the expression of

132     TREM2 was lower in LUAD(lung adenocarcinoma)、LUSC(lung squamous cell carcinoma) than

133     in their respective adjacent normal tissues.

134

135     The Relationship between TREM2 and prognosis in pan-cancer

136

137     We evaluate the expression of TREM2 via three datasets. Firstly, in PrognoScan, the results

138     showed that in 3 types of cancers, including lung, colorectal, and breast cancers, TREM2

139     expression significantly influences prognosis(Figure 2A-H). Among them, TREM2 played a

140     detrimental role in Colorectal cancer (DFS: HR=1.23, coxp=0.026; DFS: HR=2.07, Coxp=0.046).

141     Meanwhile, an interesting result can be noticed in lung cancer and breast cancer. ONE cohorts

142     (GSE31210) included 204 samples showed that low expression was notably associated with

143     better prognosis(OS HR=2.21,Coxp=0.0014;RFS HR=1.88,coxp=<0.001.), however, three

144     cohorts(GSE1321,GSE11117,GSE13213)suggest the reverse may be the case(OS HR=0.37,

145     Cox p=<0.001; OS HR=0.55,coxp=0.008; OS HR=0.72,Coxp=0.019).the opposite results can

146     also be seen in the breast cancer. One cohort (GSE1379) that included 60 samples showed

147     that high expression was notably associated with poor RFS (RFS HR=2.15, coxp=0.044), and

148     another cohort (GSE19615) showed the opposite result. (DMFS HR=0.32, Coxp=0.029).

149     Therefore, it is conceivable that low TREM2expression is an independent risk factor and leads

150     to a better prognosis in CRC patients.

151     To further examine the prognostic potential of TREM2 in different cancers, we evaluate the

152     TREM2 prognostic value based on Affymetrix microarrays via the Kaplan-Meier plotter

153     database. These results suggested that low TREM2 expression was significantly associated

154     with better prognosis in Ovarian(OS HR = 1.27 (1.09 − 1.47) log-rank P = 0.0014;PFS HR =

155  1.25 (1.04 − 1.51) log-rank P = 0.02). However, TREM2 expression has less influence on

156  Gastric cancer(Figure 3). We can also notice that the low expression of TREM2 predicts a

157  better OS in lung cancer and liver cancer, while a poor OS in breast cancer. The last, we

158  analyzed relationships between TREM2 expression and prognostic values by using the GEPIA

159  DATASET, which analyzing the RNA sequencing expression data of 33 types of cancer from

160  TCGA (Supplementary Figure 1). Low TREM2 expression levels were associated with a better

161  prognosis of OS and DFS in LGG, LIHC, OS in COAD, and DFS in PRAD. Meanwhile, LOW

162  TREM2 expression was correlated with poorer prognosis of OS in CHOL, KIRP, and SKCM.

163  These results confirmed the prognostic value of TREM2 in some specific types of cancers, and

164  that increased and decreased TREM2 expression have different prognostic value depending

165  on the type of cancer.

166

167  The correlation between trem2 expression lever and clinicopathological features

168

169  As shown in the table 1, In KIRP, those who process following characteristics has a better

170  prognosis:type2(HR=4.05,P=0.018),T2(HR=6.95,P=0.05),T2+T3(HR=3.94,P=0.02),stage

171  III(HR=4.44,P=0.01),stage II+III(HR=4.95,P=0.0048), stage III+IV(HR=2.61,P=0.0248),In age

172  and race, No significant correlation was found . moreover, the Under-expression of TREM2

173  benefited Female liver cancer patients of OS (HR=4.44, P=0.01), while benefited male of

174  PFS(HR=4.44, P=0.01). High TREM2 mRNA expression was correlated with worse OS in stages

175  2 to 4, grades 2 to 3, but was not associated with OS stage 1.

176

177    The Correlation Analysis of TREM2 and Immune Infiltration Level

178

179    The above results support the prognostic role of TREM2 in pan-cancer. Therefore, it is of

180    great significance to explore the relationship between TREM2 expression and immune

181    infiltration. TIMER got the TREM2 expression and immune infiltration level coefficient to

182    discuss their correlation in 39 cancer types. The results indicated that TREM2 expression has

183    significant correlations with tumor purity in 33 types of cancer. TREM2 expression has

184    significant correlations with B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and

185    dendritic cells. The number of tumors is 21,23,33,34,28,34, respectively. Then, we should

186    decide on the tumor. On the one hand, the effect of tumor purity should be considered. On

187    the other hand, it needs associating with TREM2 both in prognosis and immune infiltration.

188    Based on the above, we chose to focus on LIHC and KIRP. Both for LIHC and KIRP, there is a

189    strong correlation between TREM2 expression with the monocyte (LIHC: HR=0.554, P= 7.64e

190    −29 KIRP: HR=0.555, P= 1.53e−21), and Dendritic cell(LIHC: HR=0.53, P= 5.48e−26    KIRP:

191    HR=0.645, P= 1.52e−31), furthermore, the expression of TREM2 has significant weakly and

192    modestly positive correlations with infiltrating levels of the B cell, CD8+ T cells, CD4+ T cells,

193    and neutrophils in LIHC and KIRP, those results showed in figure4. Those results implicated

194    that TREM2 plays a significant role in immune infiltration in LIHC and KIRP, especially

195    macrophages and DCs.

196    TREM2 expression is associated with Immune Marker Sets

197    To study the relationship between TREM2 and the various immune infiltrating cells, we

198    concentrated on the correlations between TREM2 and immune marker sets of assorted

199 immune cells in KIRP and LIHC within the TIMER and GEPIA databases. Various immune

200 marker genes of immune cells mentioned below were studied, such as CD8+ T cells, T cells

201 (general), B cells, monocytes, TAMs, M1 and M2 macrophages, neutrophils, and NK. Cells as

202 well as DCs. Different functional T cells were also studied, included Th1 cells, Th2 cells, Tfh

203 cells, Th17 cells, Tregs, and exhausted T cells. The results adjustment by purity revealed that

204 the expression of TREM2 was significantly positively correlated with most immune marker sets

205 in KIRP and LIHC, Specifically monocytes andDCs. It is worth noting that some difference in

206 results between KIRP and LIHC (Table 2 and Figures 5). We found that TREM2 expression is

207 associated with CD8+ T cell markers, challenging to be detected in KIRP.

208 Similarly, the expression of TREM2 has strong correlations with Treg and T cell exhaustion in

209 LIHC. However, these two types were less significant in another. The details are as follows. For

210 CD8+T cells, we can find a positive correlation between TREM2 expression and CD8A and

211 CD8B in KIRP. For DC cell, including HLA-DPB1, HLA-DQB1, HLA-DRA, HLA-DPA1, CD11c,

212 those markers are positively strong related with TREM2 expression both in KIRP and LIHC. for

213 Treg cells and T cell exhaustion, In KIRP, TREM2 has an only positive correlation with the TIM-

214 3, in LIHC, the trem2 expression has a strong association with the markers, including CCR8,

215 TGFB1, PD-1, CTLA4, TIM-3. DCs play a central role in regulating the balance between CD8

216 T cell immunity and tumor antigen tolerance. It can promote activated CD8+ T cells and be

217 controlled by TME, enabling tumor development[19]. Treg cells participate in the occurrence

218 and development of tumors by inhibiting anti-tumor immunity[20]. 'T cells exhaustion ' refers

219 to the gradual deterioration of CD8+ T cells function when cells are exposed to antigens or

220 inflammatory signals for a long time. The expression of multiple inhibitory receptors (such as

221  PD-1 and LAG3) is the characteristic of exhausted T cells[21]. We further verify the results with

222  the GEPIA database. We found that the results are similar to those in TIMER (Table 3). These

223  results also reveal that TREM2 plays a vital role in the microenvironment.

224

225  **Discussion**

226  For a long time, people have devoted themselves to studying the role of immune receptor

227  TREM2 in human neurodegenerative diseases. In recent years, many researchers have tried

228  to explore the relationship between TREM2 and tumors. TREM2 has been confirmed as a

229  marker for tumor-associated macrophages (TAMs) and monocytes [22]. Research reports

230  that TREM2 is a Tumor Suppressor in Colorectal Carcinoma and Exert negative

231  immunomodulatory function in lung cancer[23] [24].however, the role of TREM2 expression

232  has not been elucidated in KIRP.

233  In this study, we explore what role TREM2 played in tumor prognosis and

234  tumor microenvironment. We use Oncomine datasets to analyze TREM2 expression via three

235  datasets to find further information about prognosis. Our results indicated that TREM2 mRNA

236  expression is higher in bladder cancer, brain and CNS cancer, breast cancer, cervical cancer,

237  colorectal cancer, esophageal cancer, stomach cancer, head and neck, kidney cancer,

238  pancreatic cancer, and prostate cancer. But it is lower in lung cancer. Analysis of the TCGA

239  data showed that TREM2 expression was higher in BLCA、BRCA、CESC、CHOL、COAD、

240  GBM、HNSC、KICH、KIRC、KIRP、LIHC、PRAD、STAD、THCA、UCEC, but the lower expression

241  in LUAD and LUSC compared with normal adjacent tissues. We can easily find that the results

242  are highly consistent. By analyzing the results from several datasets, we found that the high

243 expression of TREM2 may indicate poor prognosis in colorectal cancer, ovarian cancer, lower-

244 grade Glioma, and liver cancer. We also found that TREM2 overexpression may predict a

245 better prognosis in KIRP. We also pay more attention to Kidney renal papillary cell carcinoma

246 (KIRP) patients, meanwhile using liver hepatocellular carcinoma (LIHC)as the control. The

247 relationship between TREM2 mRNA level and clinicopathological features in patients with Kirp

248 and LIHC was investigated using bioinformatics. The result suggested that low TREM2

249 expression levels were significantly correlated with tumor type, higher T stage, and higher

250 TNM stage in KIRP. On the contrary, high TREM2 expression levels were significantly

251 associated with tumor type, higher T stage, higher TNM stage, and higher GRADE in LIHC. It

252 has been described in articles that TREM2 is a new type of tumor suppressor gene for liver

253 cancer, and the decreased expression of TREM2 in HCC patients is associated with poor

254 prognosis[25] .the results are consistent. We conclude that high TREM2 expression may can

255 as an independent prognostic factor for KIRP and liver patients.

256 Finally, we use TIMER to explore the relationship between TREM2 and diverse immune

257 infiltration levels in cancer. Our results indicate a strong positive correlation between the

258 expression level of TREM2 and the level of macrophages and dendritic cell infiltration, a

259 modest positive correlation in other infiltration levels (B cells, CD8+ T cells, CD4+ T cells, and

260 neutrophils) both in KIRP and LIHC. To further explore the reasons for the different results,

261 We investigated the correlation between immune cell marker genes and TREM2 expression.

262 The same point is that the rise in expression of TREM2 is positively associated with the

263 expression of markers of T cell, monocyte, TAM, m2 Macrophage, and DC cell both in KIRP

264 and LIHC. The slightly noticeable difference is that a modest positive correlation between the

265 expression level of TREM2 and the level of CD8+Tcell, but it does not correlate with Treg and

266 T cell exhaustion markers expression in KIRP.

267 Furthermore, The rise in expression of TREM2 is positively associated with the expression of

268 markers of Treg and T cell exhaustion in LIHC. These results from TIMER datasets are after

269 purity correction. We further verified the accuracy of the results with the GEPIA

270 database.  Some researches indicated that high TREM2 expression predicts poor prognosis

271 in other tumors like Glioma, mammary tumors, and colorectal cancer. According to our result,

272 We still have reason to believe that high TREM2 expression has a better prognosis in KIRP.

273 These results may be related to the differential immune infiltration of different tumors. Also,

274 Different tumors have other mechanisms that play a significant role. It was already mentioned

275 above that the effects of TREM2 in modulating tumor immunology may be achieved by DC

276 cell and M2 macrophage in KIRP and LIHC. Dendritic cells (DC) play a central role in regulating

277 the balance between CD8 T cell immunity and tumor antigen tolerance, while M2

278 macrophages suppress intratumoral CD8+ T cell recruitment [19]. According to the difference

279 of results, we can boldly speculate that CD8 T cells activated by DC through cross-

280 presentation of exogenous antigen may be dominant in KIRP. At the same time, M2

281 macrophage and TREG may play the leading role. It may be the starting point for our next

282 experimental study.

283 In summary, increased TREM2 expression correlates with a better prognosis in KIRP. Both in

284 KIRP and LIHC, TREM2 expression potentially contributes to the regulation of T cell,

285 monocyte, TAM, M2 macrophage, and DCs. Besides, in KIRP, TREM2 expression may

286 participate in the regulation of CD8+Tcell in KIRP while regulating Treg in LIHC. Therefore,

287    TREM2 likely plays an essential role in immune cell infiltration and can as a potential

288    prognosis biomarker in KIRP.

289

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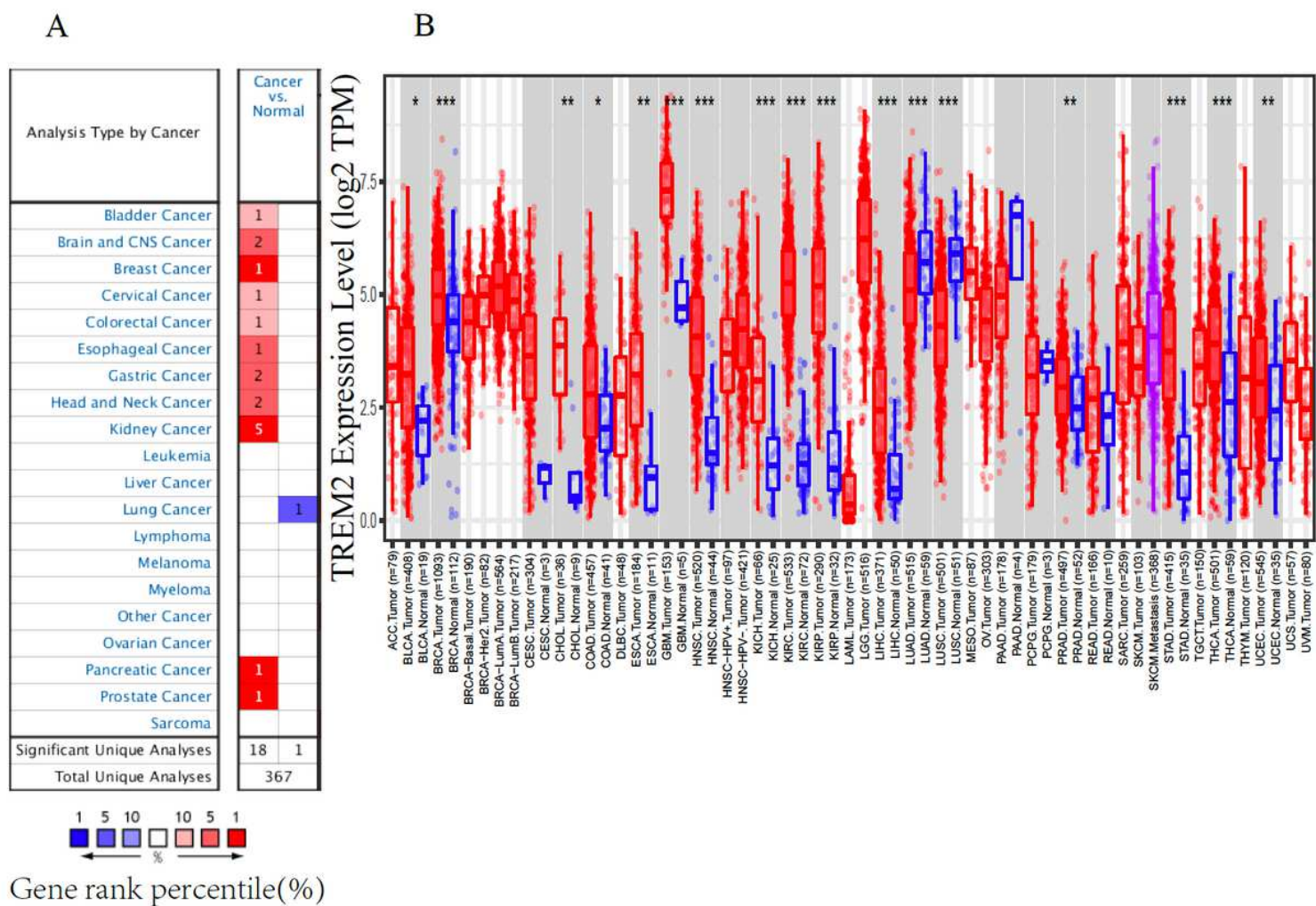
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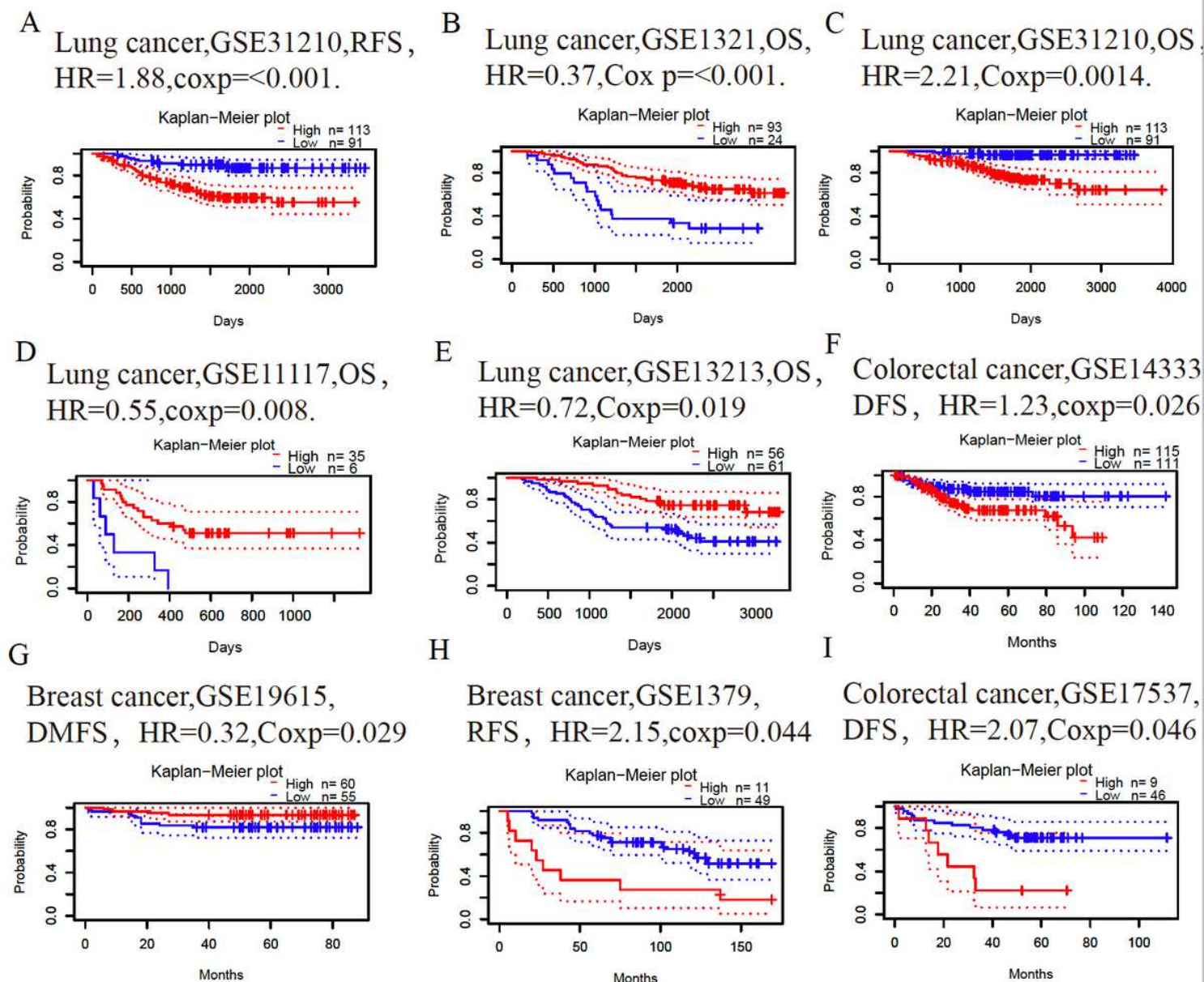# Figures



## Figure 1

Caption not available with this version
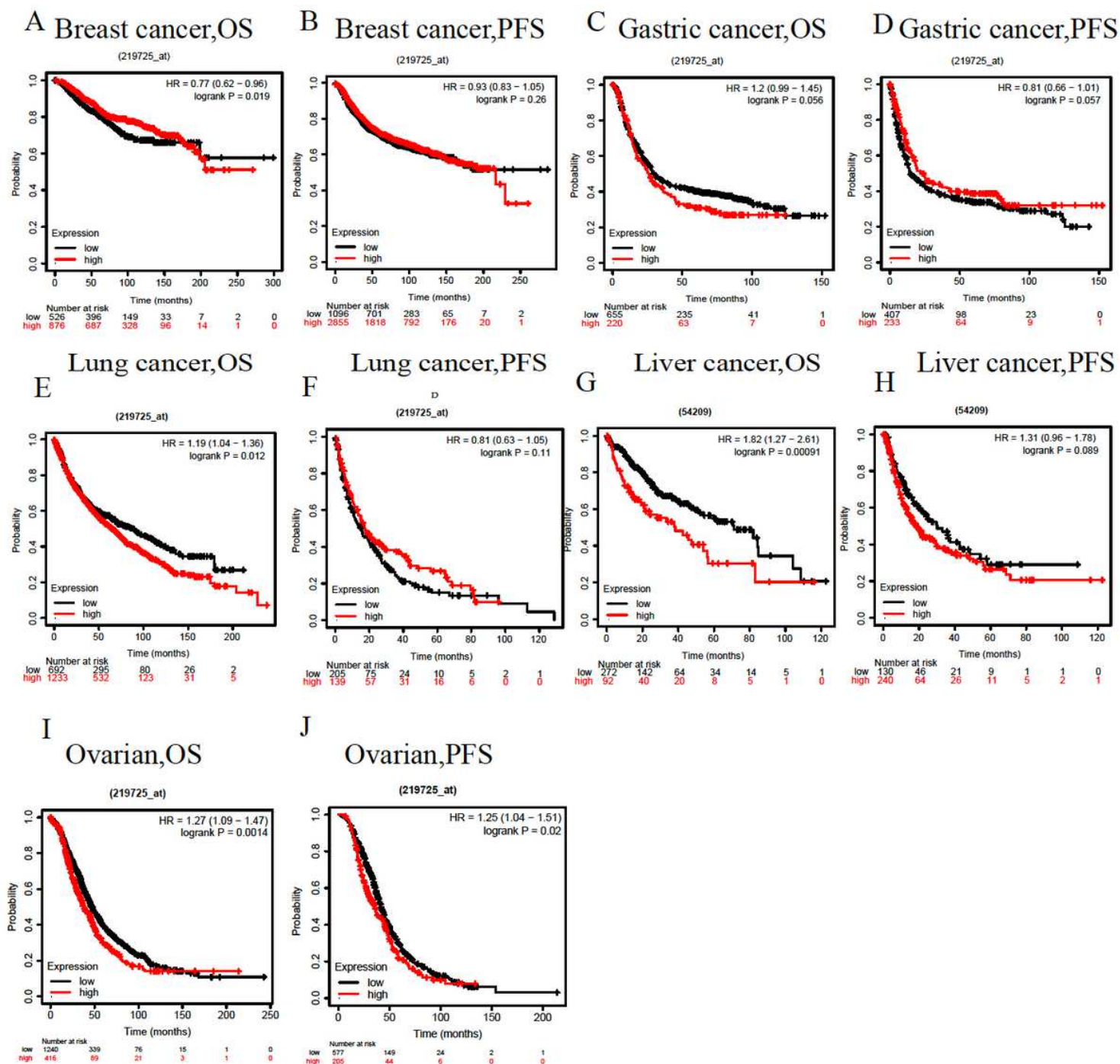
**Figure 2**

Caption not available with this version

**Figure 3**
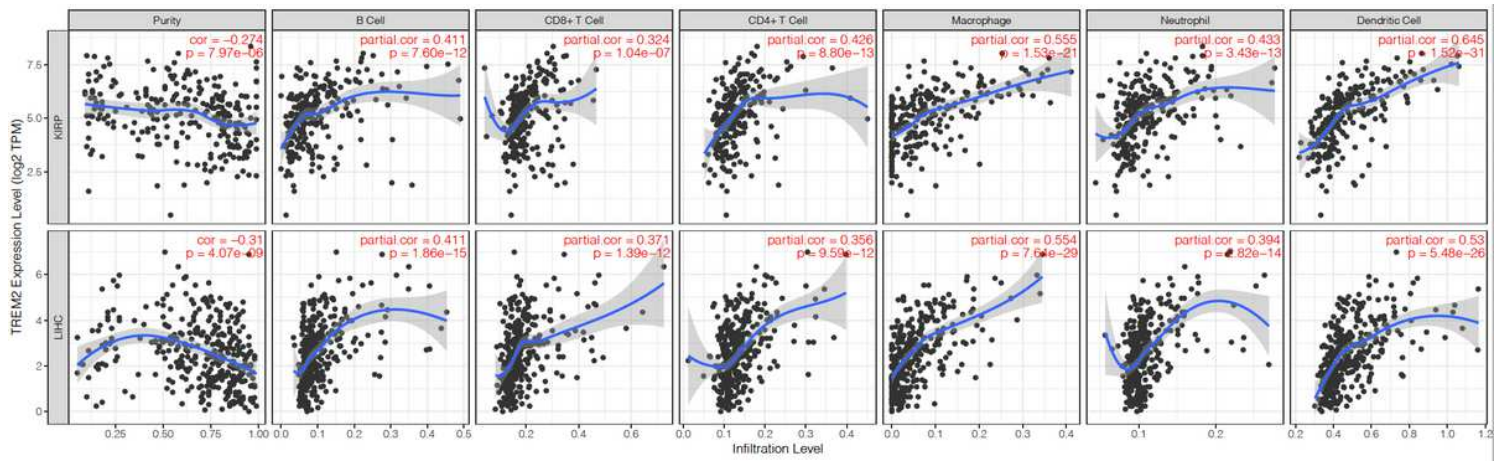
Caption not available with this version

**Figure 4**

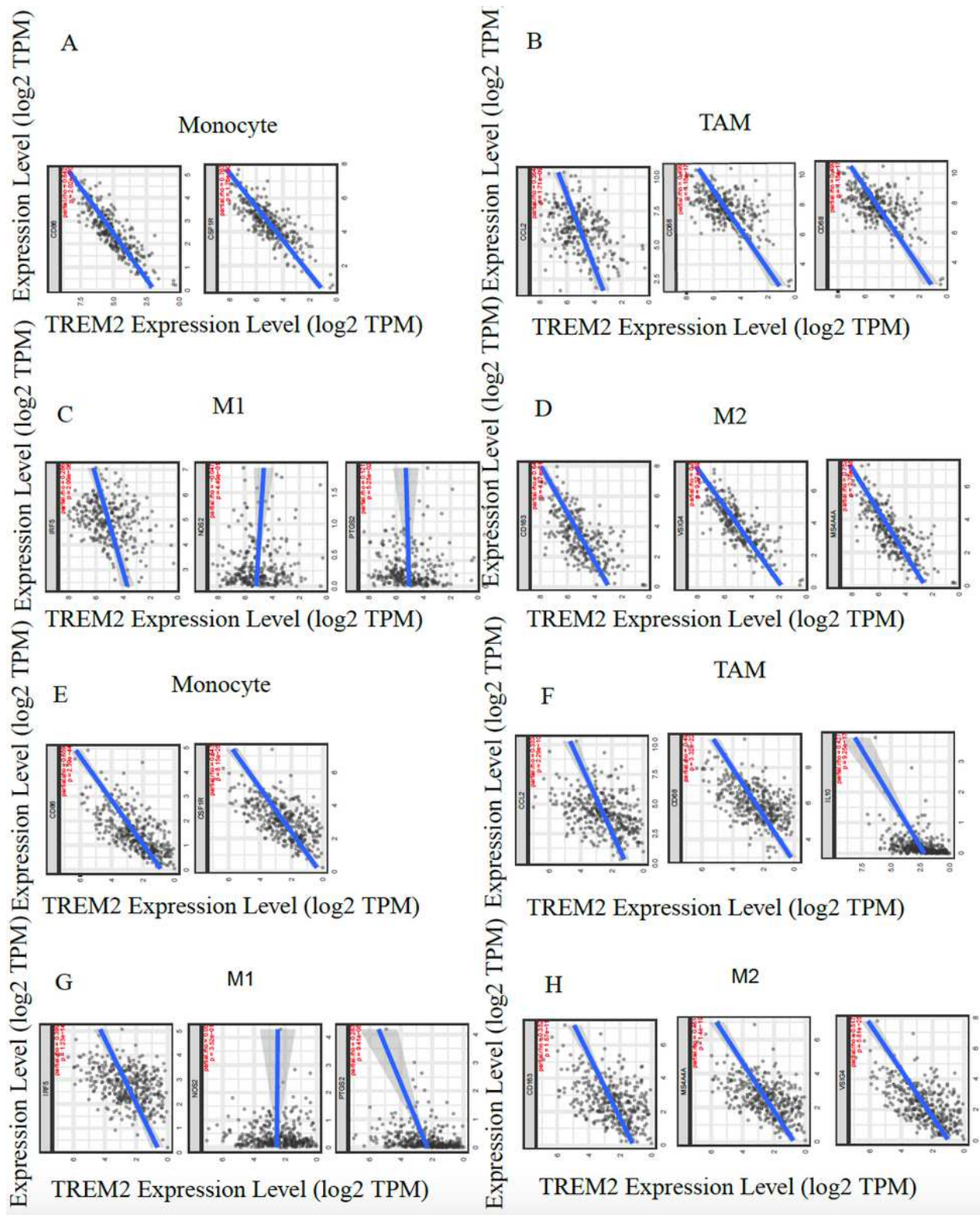Caption not available with this version

**Figure 5**

Caption not available with this version

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
- Table2.xlsx
- Table3.xlsx
- SupplementaryFigure1.1.pdf
- SupplementaryFigure1.2.pdf
- SupplementaryFigure1.3.pdf
- SupplementaryFigure1.4.pdf
- SupplementaryFigure2.pdf
- SupplementaryTable1.xlsx