

# Prognostic roles of mRNA expression of peroxiredoxins in lung cancer

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**Background:** The peroxiredoxin (PRDX) protein family is involved in cancer cell invasion and metastasis, but its prognostic value in lung cancer remain elusive.

**Methods:** In this report, we accessed the overall survival (OS) of each individual *PRDX* mRNA expression through the Kaplan–Meier plotter (KM plotter) database, in which updated gene expression data and survival information include a total of 1,926 lung cancer patients.

**Results:** Our results indicated that *PRDX1* and *PRDX2* mRNA expressions were associated with improved OS in all lung cancer patients especially in lung adenocarcinoma patients, whereas *PRDX5* and *PRDX6* mRNA expressions were associated with poor OS in all lung cancer patients. In addition, the prognostic value of PRDXs in the different clinicopathological features according to smoking status, pathological grades, clinical stages, and chemotherapeutic treatment of lung cancer patients was further assessed in the KM plotter database by the multivariate cox regression analysis.

**Conclusion:** Our finding will elucidate the prognostic role of PRDXs in lung cancer and might promote development of PRDX-targeted inhibitors for the treatment of lung cancer.

**Keywords:** PRDX, expression, prognostic, KM plotter, smoking status, lung cancer

## Introduction

Lung cancer is one of the most common cancers and the leading cause of cancer death worldwide. It is generally classified as small-cell lung cancer and non-small-cell lung cancer (NSCLC), accounting for 15% and 85% of all lung cancers, respectively.<sup>1</sup> NSCLC includes adenocarcinoma (Ade), squamous cell carcinoma (SCC) and large cell carcinoma. While standard treatment and better supportive care have improved overall survival (OS) and life quality, the prognosis of lung cancer is still unfavorable with an overall 5-year survival rate <15%.<sup>2</sup> Therefore, there is much interest in identifying a more accurate prognostic assessment and molecular biomarkers for lung cancer.

Peroxiredoxins (PRDXs) are a ubiquitous family of small (22–27 kDa) non-seleno peroxidases which catalyze peroxide reduction to balance cellular hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) levels.<sup>3,4</sup> They are divided into two classes: 2-Cys PRDXs and 1-Cys PRDX. Six PRDX isoforms have been identified.<sup>5</sup> Increased or decreased levels of PRDXs have been demonstrated in many human cancers.<sup>6–10</sup> Studies performed in vitro or in vivo models have demonstrated that overexpression of PRDXs may either inhibit cancer development or promote cancer growth, depending on the specific PRDX family member and on the cancer context.<sup>11–15</sup> However, the prognostic value of mRNA expression of individual *PRDXs* in lung cancer patients is still elusive. In this study, we determined the prognostic roles of mRNA expression of six *PRDXs* in lung cancer patients.

KM plotter database generated data from The European Genome-phenome Archive (EGA), Gene Expression Omnibus (GEO), and The Cancer Genome Atlas (TCGA,

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<http://cancergenome.nih.gov>) cancer data sets,<sup>16</sup> which include gene expression data and survival information from a total of 1,926 lung cancer patients. In the present study, we used the KM plotter database and accessed the prognostic roles of individual *PRDX* mRNA expression in patients with lung cancer.

## Materials and methods

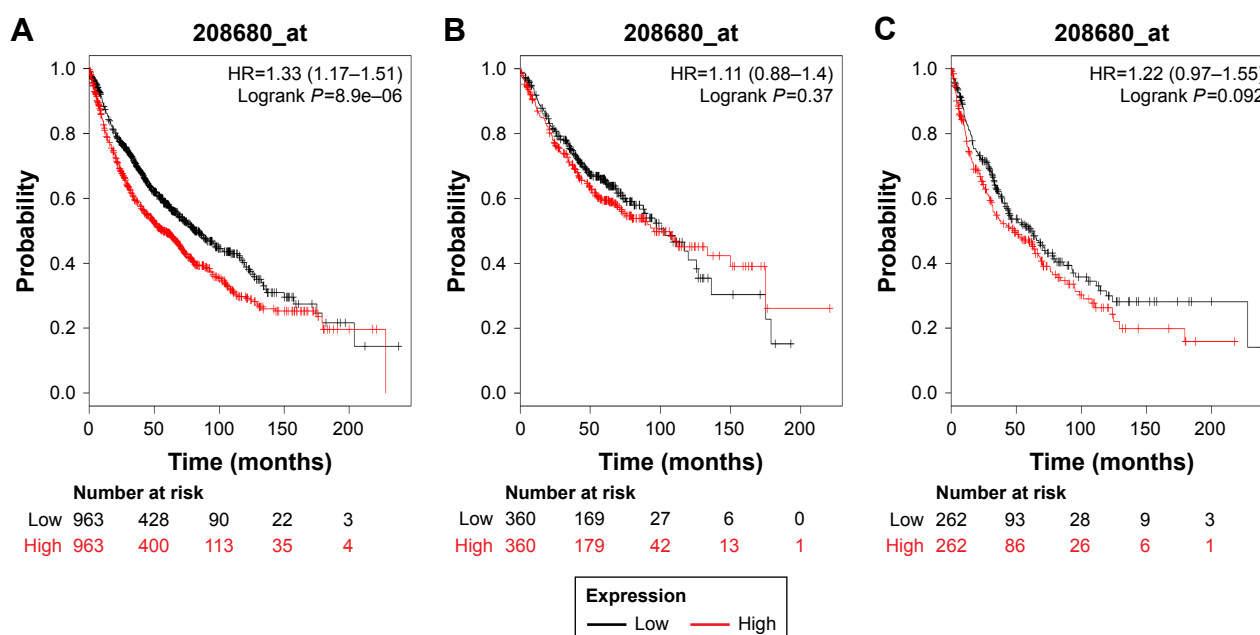
The Kaplan–Meier plotter (KM plotter, <http://kmplot.com/analysis/>) has information of 54,675 genes on survival using 10,461 cancer samples, which include breast,<sup>17</sup> ovarian,<sup>18</sup> gastric,<sup>19</sup> and lung<sup>16</sup> cancer patients with a mean follow-up of 69, 40, 49, and 33 months, respectively. Gene expression data and OS information are downloaded from EGA, GEO (Affymetrix microarrays only), and TCGA, which is handled by a PostgreSQL server and integrates clinical data and gene expression information simultaneously. The database collected survival information of 1,926 lung cancer patients, which comprises clinical data such as gender, age, histology, grade, stage, and chemotherapy of all patients in WinStat 2013.<sup>16</sup>

In our study, the prognostic values of the individual mRNA expression of *PRDXs* in lung cancer were speculated using the KM plotter online database. In addition, we evaluated the correlation between OS of lung cancer patients and specific *PRDXs* based on smoking status, pathological grades, clinical stages, and chemotherapeutic treatment. Briefly, the JetSet probe IDs representing the six genes of *PRDXs* (*PRDX1*, *PRDX2*, *PRDX3*, *PRDX4*, *PRDX5*, and

*PRDX6*) individually entered into the database (<http://kmplot.com/analysis/index.php?p=service&cancer=lung>) to analyze Kaplan–Meier survival curves. With the purpose to determine the prognostic value of a particular gene, certain gene mRNA expression between the lower and upper quartiles were computed, and the best performing threshold was used as the final cutoff in a univariate cox regression analysis. Smoking status, pathological grades, clinical stages, and chemotherapeutic treatment were calculated in the multivariate analysis. Finally, the expression cutoff points of the *PRDX* genes were determined according to the median expression of the gene from the selected lung cancer samples. *PRDX* expression were split into “low” and “high” depending on the comparisons between expression values with established cutoffs. The number of cases, median values of mRNA expression levels, HR, 95% CI, and log rank *P* were determined and presented on the webpage. *P*-value of <0.05 was deemed to be statistically significant to reduce the false-positive rate.

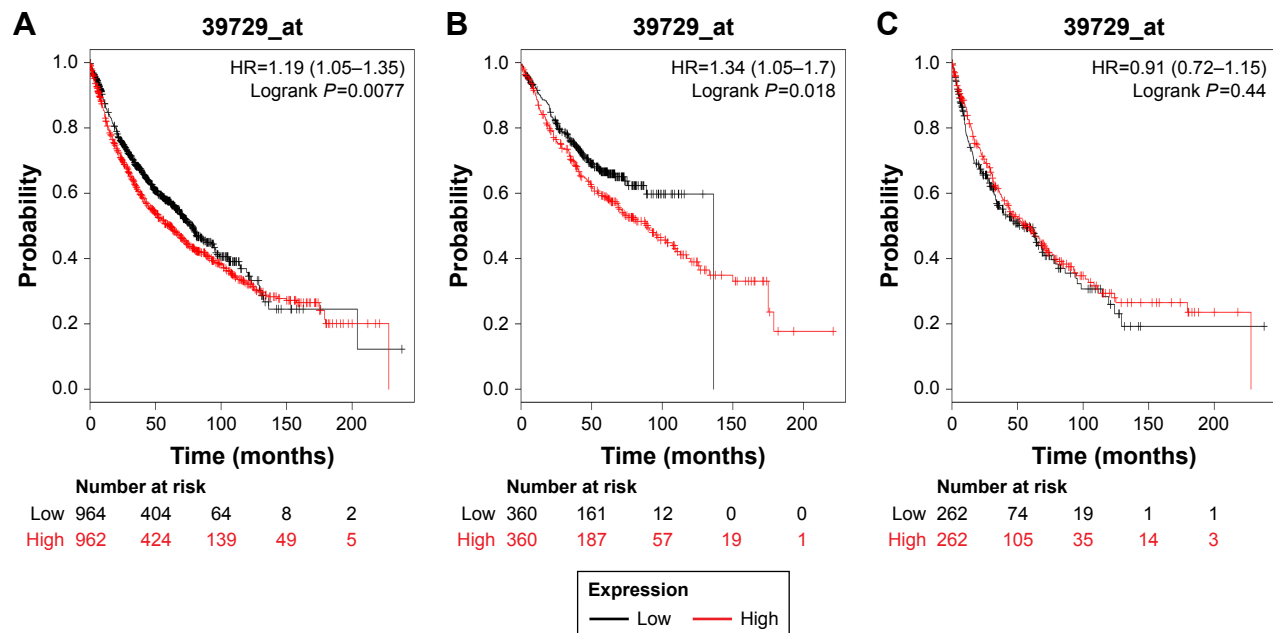
## Results

In our present study, all the six *PRDX* family Kaplan–Meier survival information can be determined on [www.kmplot.com](http://www.kmplot.com). We used KM plotter and determined the prognostic value of *PRDX1* in the database. The valid Affymetrix ID is 208680\_at (*PRDX1*). Survival curves are drafted for all lung cancer patients (*n*=1,926) (Figure 1A), Ade patients (*n*=720) (Figure 1B), and SCC patients (*n*=524) (Figure 1C). *PRDX1* mRNA high expression was correlated with worse OS for



**Figure 1** The prognostic value of *PRDX1* expression in the database.

**Notes:** The valid Affymetrix ID is 208680\_at (*PRDX1*). Survival curves are plotted for (A) all patients (*n*=1,926), HR=1.33 (95% CI: 1.17–1.51); (B) adenocarcinoma (*n*=720), HR=1.11 (95% CI: 0.88–1.4); and (C) squamous cell carcinoma (*n*=524), HR=1.22 (95% CI: 0.97–1.55).



**Figure 2** The prognostic value of *PRDX2* expression in the database.

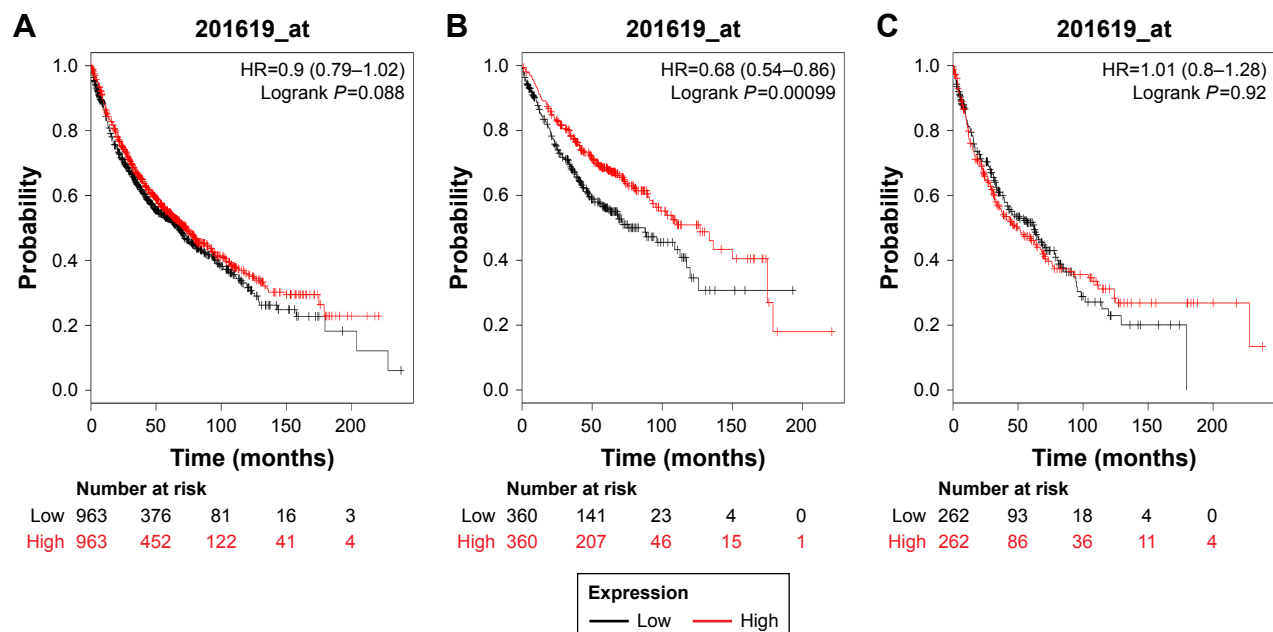
**Notes:** The valid Affymetrix ID is 39729\_at (*PRDX2*). Survival curves are plotted for (A) all patients ( $n=1,926$ ), HR=1.19 (95% CI: 1.05–1.35); (B) adenocarcinoma ( $n=720$ ), HR=1.34 (95% CI: 1.05–1.7); and (C) squamous cell carcinoma ( $n=524$ ), HR=0.91 (95% CI: 0.72–1.15).

all lung cancer patients who were followed for 20 years (HR=1.33, 95% CI: 1.17–1.51,  $P=8.9\text{e-}6$ ). Nevertheless, with regard to Ade and SCC patients, there was no significant difference in HR estimates between study strata.

We next determined the prognostic value of *PRDX2* in the database. The valid Affymetrix ID is 39729\_at (*PRDX2*). *PRDX2* mRNA high expression was significantly correlated

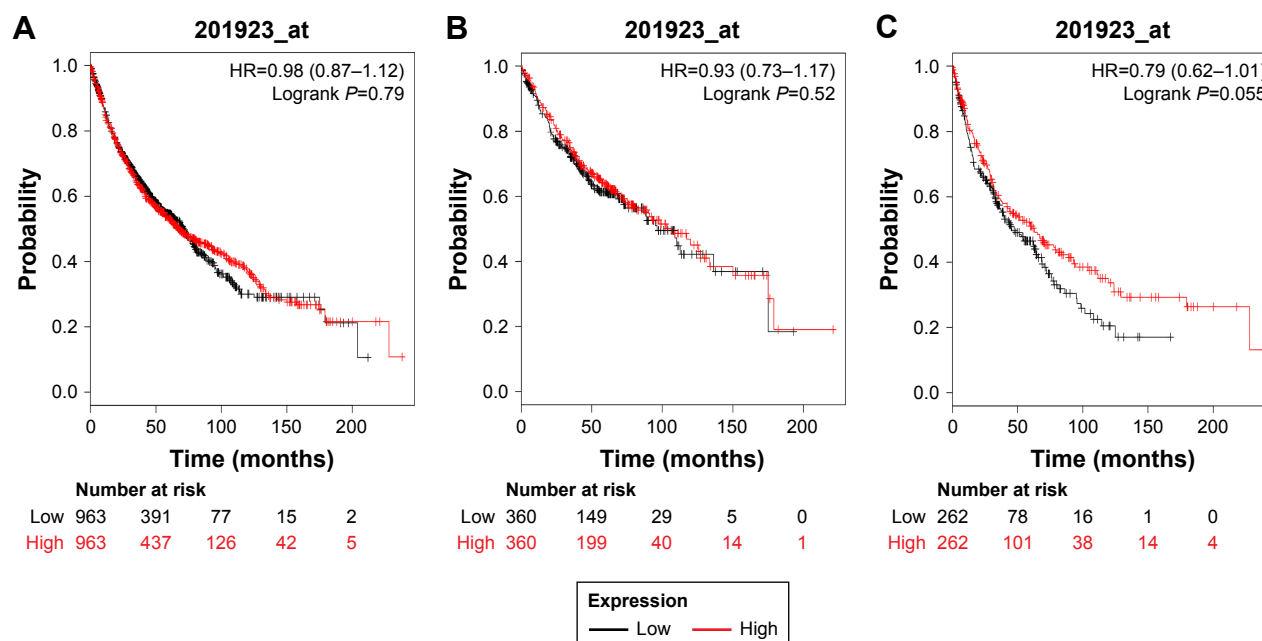
with worse OS for all patients (HR=1.19, 95% CI: 1.05–1.35,  $P=0.0077$ ; Figure 2A). *PRDX2* mRNA high expression was also correlated with worse OS in Ade patients (HR=1.34, 95% CI: 1.05–1.7,  $P=0.018$ ; Figure 2B), but not in SCC patients (HR=0.91, 95% CI: 0.72–1.15,  $P=0.44$ ; Figure 2C).

Figure 3 demonstrates the prognostic value of *PRDX3* in the database. The valid Affymetrix ID is 201619\_at



**Figure 3** The prognostic value of *PRDX3* expression in the database.

**Notes:** The valid Affymetrix ID is 201619\_at (*PRDX3*). Survival curves are plotted for (A) all patients ( $n=1,926$ ), HR=0.88 (95% CI: 0.79–1.02); (B) adenocarcinoma ( $n=720$ ), HR=0.68 (95% CI: 0.54–0.86); and (C) squamous cell carcinoma ( $n=524$ ), HR=1.01 (95% CI: 0.8–1.28).



**Figure 4** The prognostic value of *PRDX4* expression in the database.

**Notes:** The valid Affymetrix ID is 201923\_at (*PRDX4*). Survival curves are plotted for (A) all patients (n=1,926), HR=0.95 (95% CI: 0.87–1.12); (B) adenocarcinoma (n=720), HR=0.93 (95% CI: 0.73–1.17); (C) squamous cell carcinoma (n=524), HR=0.79 (95% CI: 0.62–1.01).

(*PRDX3*). *PRDX3* mRNA high expression was not significantly correlated with OS for all lung cancer patients (HR=0.9, 95% CI: 0.79–1.02,  $P=0.088$ ; Figure 3A), SCC patients (HR=1.01, 95% CI: 0.8–1.28,  $P=0.9174$ ; Figure 3B). However, *PRDX3* mRNA expression predicted a better OS in Ade patients (HR=0.68, 95% CI: 0.54–0.86,  $P=0.0011$ ; Figure 3C).

Figure 4 shows the prognostic value of *PRDX4* in the database. The valid Affymetrix ID is 201923\_at (*PRDX4*). *PRDX4* mRNA high expression was not significantly correlated with OS for all lung cancer patients (HR=0.98, 95% CI: 0.87–1.12,  $P=0.79$ ; Figure 4A), Ade patients (HR=0.93, 95% CI: 0.73–1.17,  $P=0.5238$ ; Figure 4B), as well as patients with SCC (HR=0.79, 95% CI: 0.62–1.01,  $P=0.0556$ ; Figure 4C).

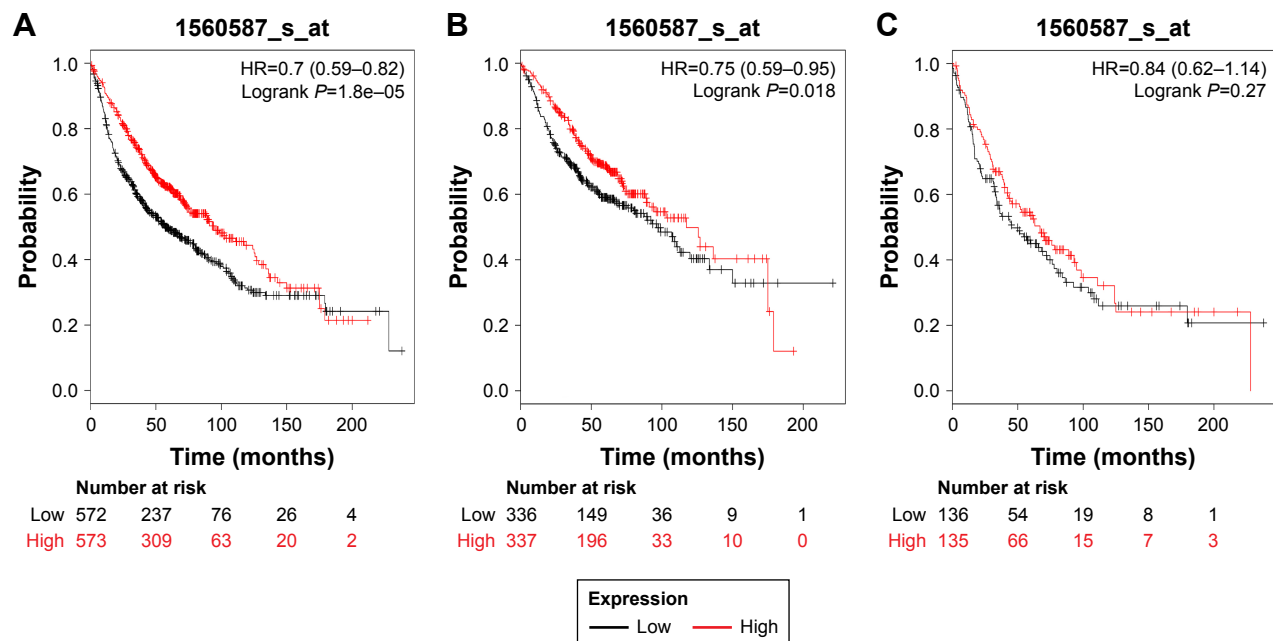
Figures 5 and 6 present the prognostic significance of *PRDX5* and *PRDX6*, respectively. Affymetrix IDs were as follows: 1560587\_s\_at (*PRDX5*) and 200845\_s\_at (*PRDX6*). Both elevated *PRDX5* and *PRDX6* mRNA expressions are associated with a favorable OS for all the lung cancer patients (*PRDX5*: HR=0.7, 95% CI: 0.59–0.82,  $P=1.8\text{e-}5$ , Figure 5A; *PRDX6*: HR=0.71, 95% CI: 0.63–0.81,  $P=1.5\text{e-}7$ , Figure 6A). In addition, only *PRDX6* mRNA high expression was significantly associated with worse OS in Ade patients (HR=0.45, 95% CI: 0.35–0.57,  $P=2.8\text{e-}11$ ).

To further assess the association of PRDXs with other clinicopathological profiles, we determined the correlation with the patients' smoking status (Table 1), clinical different

stages (Table 2), and chemotherapeutic treatment. As from Table 1, *PRDX1* and *PRDX6* are significantly correlated with the smoking status. *PRDX3* and *PRDX6* are significantly associated with lung cancer patients without smoking history. From Table 2, *PRDX1*, *PRDX2*, *PRDX3*, and *PRDX6* are significantly correlated with clinical stage I of the patients. Only *PRDX6* is significantly associated with clinical stage II of lung cancer patients. However, none of the PRDXs was associated with chemotherapy of lung cancer patients.

## Discussion

*PRDX1* was first reported as an antioxidant enzyme.<sup>20</sup> Recent studies have shown that abnormal expression of *PRDX1* has been observed in several human cancers, including breast, esophageal, liver, lung, and prostate cancers.<sup>21–24</sup> *PRDX1* is expressed at significantly higher levels in lung cancer tissues compared with normal lung tissues, and elevated *PRDX1* associated with shorter survival in lung cancer.<sup>25,26</sup> Furthermore, *PRDX1* is upregulated in NSCLC tissue interstitial fluid, and high level of *PRDX1* expression is related to lymph node metastasis and tumor differentiation.<sup>27</sup> Knockdown of *PRDX1* in lung cancer cells significantly inhibits TGF- $\beta$ 1-induced epithelial-mesenchymal transition (EMT) and cell migration, whereas *PRDX1* overexpression enhances TGF- $\beta$ 1-induced EMT and cell migration.<sup>28</sup> In addition, in vivo studies have shown that silencing of *PRDX1* leads to tumor suppression of growth and metastases by reducing the activation of c-Jun.<sup>12</sup>



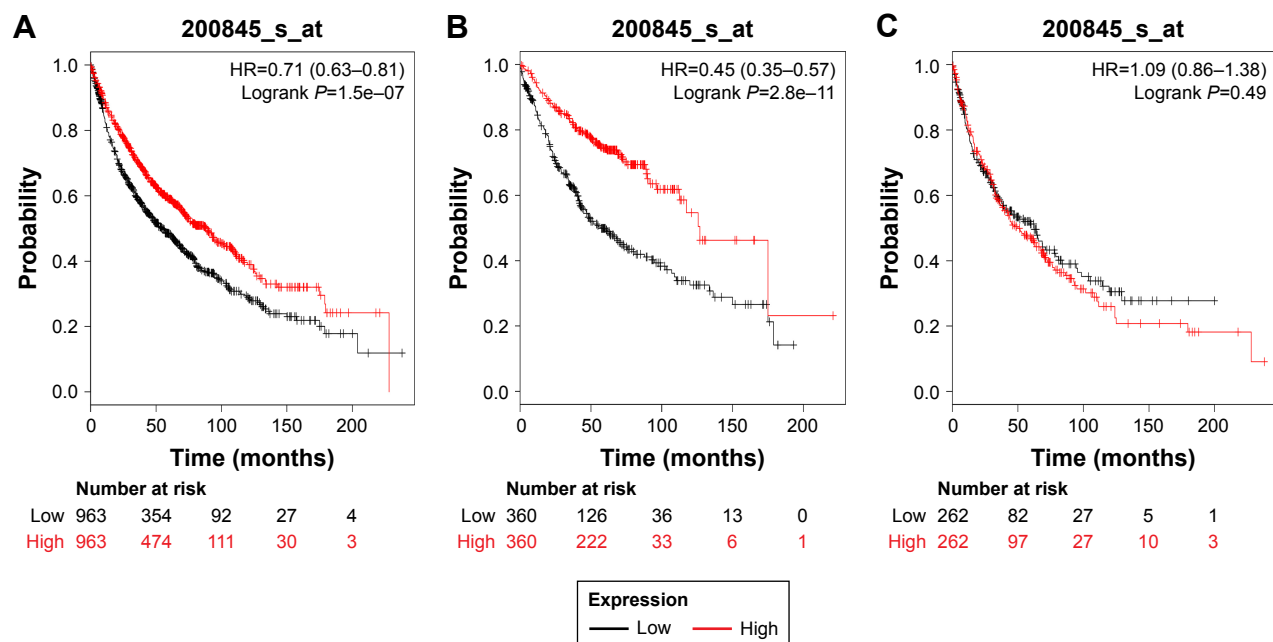
**Figure 5** The prognostic value of *PRDX5* expression in the database.

**Notes:** The valid Affymetrix ID is 1560587\_s\_at (*PRDX5*). Survival curves are plotted for (A) all patients ( $n=1,926$ ), HR=0.7 (95% CI: 0.59–0.82); (B) adenocarcinoma ( $n=720$ ), HR=0.75 (95% CI: 0.59–0.95); and (C) squamous cell carcinoma ( $n=524$ ), HR=0.84 (95% CI: 0.62–1.14).

Consistent with these findings, our data suggested that high mRNA expression of *PRDX1* was associated with worse OS in patients with stage I lung cancer. Furthermore, *PRDX1* is significantly correlated with the smoking status of patient with lung cancer.

*PRDX2*, also named as NKEF-B, was the most homologous molecule of *PRDX1* and showed similar cellular

localization.<sup>29</sup> Lu et al demonstrated that *PRDX2* overexpression in colorectal cancer tissues was strongly correlated with a more aggressive cancer behavior, tumor metastasis, and the tumor–node–metastasis (TNM) stage.<sup>30,31</sup> *PRDX2* overexpression was an independent prognostic indicator for stage I–III colorectal cancer patients.<sup>32</sup> However, the biologic role and the prognostic effect of *PRDX2* in lung cancer



**Figure 6** The prognostic value of *PRDX6* expression in the database.

**Notes:** The valid Affymetrix ID is 200845\_s\_at (*PRDX6*). Survival curves are plotted for (A) all patients ( $n=1,926$ ), HR=0.71 (95% CI: 0.63–0.81); (B) adenocarcinoma ( $n=720$ ), HR=0.45 (95% CI: 0.35–0.57); (C) squamous cell carcinoma ( $n=524$ ), HR=1.09 (95% CI: 0.86–1.38).



**Table 1** Correlation of *PRDX* mRNA expression with smoking status of lung cancer patients

Gene	Smoking history	HR (95% CI)	Log rank P
<i>PRDX1</i>	Smoke	1.24 (1.01–1.53)	0.039*
	Never smoke	1.17 (0.67–2.05)	0.5783
<i>PRDX2</i>	Smoke	1.08 (0.87–1.32)	0.4917
	Never smoke	1.3 (0.75–2.28)	0.35
<i>PRDX3</i>	Smoke	1.14 (0.92–1.4)	0.2282
	Never smoke	0.34 (0.18–0.63)	0.00035*
<i>PRDX4</i>	Smoke	0.89 (0.72–1.09)	0.26
	Never smoke	1.08 (0.62–1.87)	0.7966
<i>PRDX5</i>	Smoke	0.91 (0.61–1.37)	0.6625
	Never smoke	2.17 (0.93–5.06)	0.067
<i>PRDX6</i>	Smoke	0.72 (0.58–0.89)	0.002*
	Never smoke	0.33 (0.18–0.62)	0.00028*

Note: \* $P < 0.05$ .

Abbreviation: PRDX, peroxiredoxin.

are poorly understood. According to our results, increased mRNA expression of *PRDX2* was correlated with worse OS in all lung cancer patients as well as Ade patients, but not in SCC patients. Furthermore, high mRNA expression of *PRDX2* was associated with worse OS in stage I lung cancer patients. Additional studies are needed to explore the mechanism of PRDX2 in lung cancer.

PRDX3 was mainly located in mitochondria. Several studies have indicated that PRDX3 is overexpressed in

**Table 2** Correlation of *PRDX* mRNA expression with clinical stages of lung cancer patients

Gene	Clinical stages	HR (95% CI)	Log rank P
<i>PRDX1</i>	I	1.7 (1.29–2.24)	0.0002*
	II	1.39 (0.96–2)	0.0812
	III	1.04 (0.6–1.79)	0.8903
<i>PRDX2</i>	I	2.03 (1.51–2.71)	1.3e–06*
	II	1.06 (0.73–1.53)	0.753
	III	1.04 (0.6–1.8)	0.8863
<i>PRDX3</i>	I	0.73 (0.56–0.95)	0.0218*
	II	0.72 (0.5–1.04)	0.0782
	III	1.16 (0.67–1.99)	0.6013
<i>PRDX4</i>	I	1.09 (0.83–1.43)	0.5287
	II	0.81 (0.56–1.17)	0.2608
	III	0.95 (0.55–1.65)	0.8551
<i>PRDX5</i>	I	0.77 (0.56–1.05)	0.0975
	II	0.97 (0.62–1.52)	0.8819
	III	1.04 (0.5–2.17)	0.9078
<i>PRDX6</i>	I	0.59 (0.45–0.77)	0.00013*
	II	0.6 (0.42–0.87)	0.0063*
	III	1.01 (0.59–1.73)	0.9748

Note: \* $P < 0.05$ .

Abbreviation: PRDX, peroxiredoxin.

several human cancers, including lung cancer.<sup>33</sup> But its role in prognosis of lung cancer is barely explored. In the present study, overexpressed *PRDX3* mRNA only predicted a better OS in Ade patients, but not in SCC patients.

Wei et al demonstrated that Srx-PRDX4 axis plays a very important role in tumor progression and metastasis in lung cancer through the modulation of specific phosphokinase signaling.<sup>34</sup> However, our results showed that PRDX4 was not significantly related to OS in patients with lung cancer.

Increased levels of PRDX5 have been reported in breast cancer and malignant mesothelioma.<sup>35,36</sup> PRDX5 overexpression was associated with larger tumor size, positive lymph node status, poor differentiation, and a shorter patient survival in breast cancer patients.<sup>37</sup> PRDX5 was involved in the regulation of several mitochondrial processes, which is essential in the protection of lung cancer cells against apoptosis induced by anticancer drugs.<sup>38</sup> In this report, we observed that *PRDX5*'s high mRNA expression was found to be significantly correlated with worse OS for all lung cancer patients.

PRDX6 is a bifunctional enzyme with both GSH peroxidase and phospholipase A2 activities. PRDX6 is the only mammalian 1-Cys member of the PRDX family and is expressed in all major organs with a particularly high level in lung.<sup>39</sup> Schremmer et al showed that PRDX6 expression was significantly associated with high-grade dysplasia and tumor progression in lung cancer cells.<sup>40</sup> The invasion-promoting action of PRDX6 has also been confirmed using lung cancer cells, in which upregulation of PRDX6 results in the activation of Akt via PI3K and p38 kinase, which, in turn, promotes cell invasion by inducing uPA.<sup>41</sup> Yun et al found that PRDX6 promotes lung tumor progression via its GPx and iPLA2 activities and promotes lung tumor development via activation of the JAK2/STAT3 pathway in a carcinogen-induced mouse lung tumor model.<sup>42,43</sup> Our recent study demonstrated that high mRNA expression of *PRDX6* was associated with worse OS in lung cancer patients, Ade patients, and those with early stage I–II.

## Conclusion

In our present study, we comprehensively investigated the prognostic value of six PRDX members in patients with lung cancer by using the KM plotter database. In which, we revealed that *PRDX1* and *PRDX2* mRNA expressions were associated with improved OS in all lung cancer patients especially with Ade patients, whereas *PRDX5* and *PRDX6* mRNA expressions were associated with poor OS in all lung cancer patients. The prognostic value of the PRDX protein should be further evaluated in clinical studies. Our

finding provides new insights into the prognostic functions of PRDX proteins in lung cancer and might promote the development of PRDX-targeted inhibitors for the treatment of lung cancer.

## Disclosure

The authors report no conflicts of interest in this work.

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