

# Prognostic values of aldehyde dehydrogenase I isoenzymes in ovarian cancer

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**Abstract:** Aldehyde dehydrogenase 1 (ALDH1) activity has been used as a functional stem cell marker to isolate cancer stem cells in different cancer types, including ovarian cancer. However, which ALDH1's isoenzymes are contributing to ALDH1 activity in ovarian cancer remains elusive. In addition, the prognostic value of an individual ALDH1 isoenzyme in ovarian cancer is not clear. Thus, we accessed the prognostic value of ALDH1 isoenzymes in ovarian cancer patients through the "Kaplan–Meier plotter" online database, which can be used to determine the effect of the genes on ovarian cancer prognosis. We found that high mRNA expression of five ALDH1 isoenzymes, such as *ALDH1A1*, *ALDH1A2*, *ALDH1A3*, *ALDH1B1*, and *ALDH1L1*, was not correlated with overall survival (OS) for all 1,306 ovarian cancer patients. In addition, all five of the ALDH1 isoenzymes' high mRNA expression was found to be uncorrelated with OS in serous cancer or endometrioid cancer patients. However, *ALDH1A3*'s high mRNA expression is associated with worse OS in grade II ovarian cancer patients, hazard ratio (HR) 1.53 (1.14–2.07),  $P=0.005$ . *ALDH1A2*'s high mRNA expression is significantly associated with worse OS in *TP53* wild-type ovarian cancer patients, HR 2.86 (1.56–5.08),  $P=0.00036$ . In addition, *ALDH1A3*'s high mRNA expression is significantly associated with better OS in *TP53* wild-type ovarian cancer patients, HR 0.56 (0.32–1.00),  $P=0.04$ . Our results indicate that although ALDH1 isoenzyme mRNA might not be a prognostic marker for overall ovarian cancer patients, some isoenzymes, such as *ALDH1A2* and *ALDH1A3*, might be a good prognostic marker for some types of ovarian cancer patients.

**Keywords:** ALDH1, cancer stem cell, prognosis, KM plotter, hazard ratio

## Introduction

Ovarian cancer ranks fourth among the causes of cancer deaths in women and is the seventh most common cancer in women. It was predicted that >14,030 women will die of ovarian cancer and ~22,240 new cases of ovarian cancer were diagnosed in the USA in 2013.<sup>1</sup> Most ovarian malignancies have epithelial origins<sup>2</sup> and are further grouped into histological types as follows: serous, mucinous, clear cell, endometrioid, carcinosarcoma, transitional cell tumors (Brenner tumors), mixed epithelial tumor, undifferentiated carcinoma, and others. Despite advances in early diagnosis, cytotoxic chemotherapy, radical cure operation, and targeted therapeutic treatment, there are still ~85% of ovarian cancer patients who would develop recurrent disease, after achieving a full remission following the first-line therapy.<sup>3,4</sup> Thus, the identification on the mechanism of initiation, progression, as well as investigation of differential diagnostic prognostic marker and potential drug target, is still needed and will help to provide better prognosis and individualized treatments.

Elevated aldehyde dehydrogenase 1 (ALDH1) activity has been detected in the stem cell populations of human acute myeloid leukemia, multiple myeloma, and a number

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of solid tumors.<sup>5–9</sup> A number of reports have also shown that increased ALDH1 expression was detected in some ovarian cancer cell lines<sup>10–14</sup> and ovarian tumor tissues.<sup>11,13–20</sup> Therefore, examination of ALDH1 activity shows promising results as a universal marker for both normal and malignant stem cell populations, including ovarian cancer. The ALDH1 family is composed of enzymes that contribute to the oxidation of retinol to retinoic acid in stem cell differentiation,<sup>21–23</sup> which individual ALDH1's isoenzyme is a major isoenzyme in ovarian cancer and contribute to ALDH1 activity has not been determined. Furthermore, the prognostic role of individual ALDH1 isoenzyme in ovarian cancer remains elusive. An online Kaplan–Meier plotter (KM plotter), which can be used to determine the effect of the genes on ovarian cancer prognosis, generated data from Gene Expression Omnibus ([www.ncbi.nlm.nih.gov/geo/](http://www.ncbi.nlm.nih.gov/geo/)) database. KM plotter database was initially established using data from a group of 1,809 breast cancer patients.<sup>24,25</sup> Later, this database also included gene expression data from a total of 1,306 ovarian cancer patients.<sup>26</sup> Thus, KM plotter can be utilized for the analysis of individual genes with clinical results to total survival of patients. By using KM plotter so far, a number of prognostic markers have been identified and/or validated in breast cancer,<sup>27–37</sup> lung cancer,<sup>37–40</sup> as well as ovarian cancer.<sup>37,41,42</sup> In this study, we determined the prognostic role of individual *ALDH1* isoenzymes in human ovarian cancer patients using KM plotter database.

## Materials and methods

We used the KM plotter online database<sup>24</sup> to determine the relevance of individual *ALDH1* members' messenger RNA (mRNA) expression to overall survival (OS) of ovarian cancer patients. The Hebei Medical University Institutional Review Board deemed this retrospective study exempt from ethical approval and patient consent due to patient data being de-identified. Currently, the database includes breast cancer,<sup>24</sup> lung cancer,<sup>38</sup> gastric cancer, as well as ovarian cancer<sup>26</sup> data. Ovarian cancer patients in the database were identified from the cancer Biomedical Informatics Grid (<http://cabig.cancer.gov/>, microarray samples are published in the caArray project), on The Cancer Genome Atlas (<http://cancergenome.nih.gov/>), and the Gene Expression Omnibus (<http://www.ncbi.nlm.nih.gov/geo/>) ovarian cancer datasets.<sup>26</sup> They provided clinical data, including age, histology, grade, stage, *TP53* mutation status, and applied chemotherapy for all patients in WinStat 2013. The ovarian cancer patients were followed up for 20 years. The database was integrated using gene expression data and survival information of 1,306 ovarian cancer patients. Briefly, five *ALDH1*

sub-members (*ALDH1A1*, *ALDH1A2*, *ALDH1A3*, *ALDH1B1*, and *ALDH1L1*) were entered into the database (<http://kmplot.com/analysis/index.php?p=service&cancer=ovar>) to obtain Kaplan–Meier survival plots. Certain gene mRNA expression above or below the median separates the cases into high expression and low expression. Hazard ratio (HR), 95% confidence intervals, and logrank *P* were calculated and displayed on the webpage.

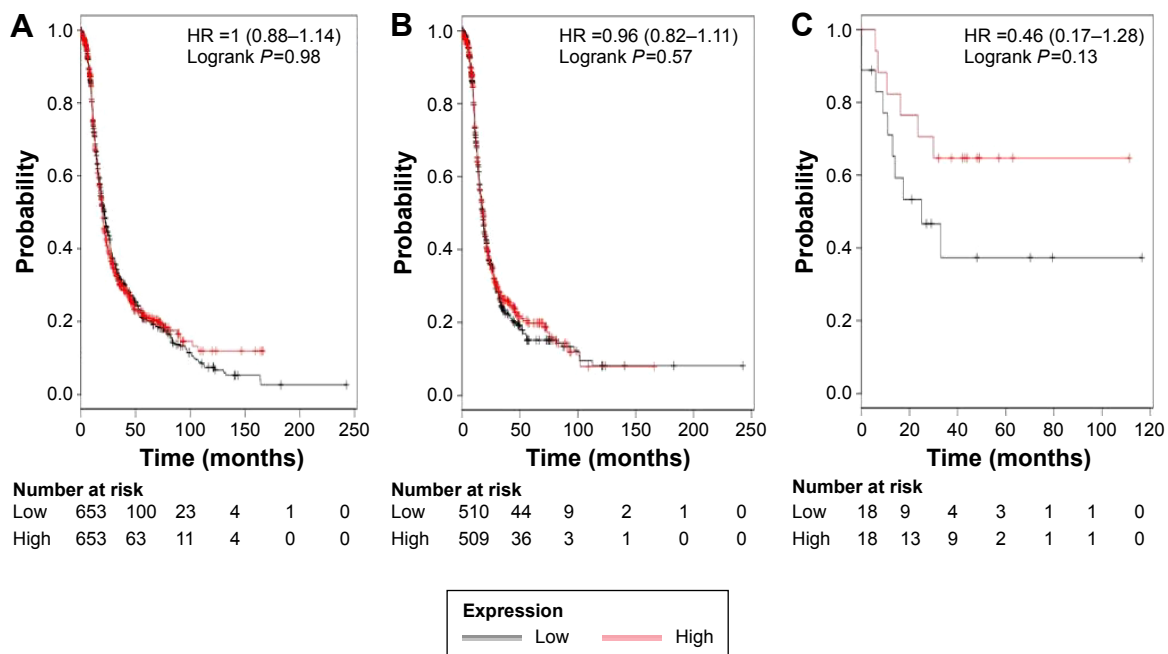
## Results

The ALDH1 family is composed of six submembers. As previously indicated,<sup>35</sup> only *ALDH1L2* among all the six ALDH1 isoenzymes was not found in [www.kmplot.com](http://www.kmplot.com), probably due to its low expression in cancer tissues. We first accessed the prognostic value of *ALDH1A1*'s mRNA expression. The desired Affymetrix ID is valid: 212224\_at (*ALDH1A1*). Survival curves are plotted for all patients (n=1,306; Figure 1A), for serous cancer patients (n=1,019; Figure 1B), and for endometrioid cancer patients (n=36; Figure 1C). *ALDH1A1*'s high mRNA expression was found to be uncorrelated with OS for all ovarian cancer patients followed for 20 years, HR 1.00 (0.77–0.99), *P*=0.98. In addition, *ALDH1A1*'s high mRNA expression was also found to be uncorrelated with OS in serous cancer patients, HR 0.96 (0.82–1.11), *P*=0.57, and in endometrioid cancer patients, HR 0.46 (0.17–1.28), *P*=0.13.

We then accessed the prognostic value of *ALDH1A2*'s mRNA expression. The desired Affymetrix ID is valid: 207015\_s\_at (*ALDH1A2*). *ALDH1A2*'s high mRNA expression was found to be uncorrelated with OS for all ovarian cancer patients, HR 1.02 (0.89–1.16), *P*=0.79 (Figure 2A). In addition, *ALDH1A2*'s high mRNA expression was also found to be uncorrelated with OS in serous cancer patients, HR 1.14 (0.98–1.33), *P*=0.087 (Figure 2B), and in endometrioid cancer patients, HR 1.17 (0.44–3.13), *P*=0.75 (Figure 2C).

Figure 3 shows the prognostic value of *ALDH1A3*'s mRNA expression. The desired Affymetrix ID is valid: 203180\_at (*ALDH1A3*). The curves show that *ALDH1A3* expression above or below the median does not separate the cases into significantly different prognostic groups in ovarian cancer patients, HR 1.08 (0.95–1.24), *P*=0.22 (Figure 3A); serous cancer patients, HR 1.13 (0.97–1.31), *P*=0.12 (Figure 3B); or endometrioid cancer patients, HR 0.41 (0.14–1.18), *P*=0.086 (Figure 3C).

Figure 4 shows the prognostic value of *ALDH1B1*'s mRNA expression. The desired Affymetrix ID is valid: 209646\_x\_at (*ALDH1B1*). *ALDH1B1*'s high mRNA expression was found to be uncorrelated with OS for all ovarian cancer patients, HR 1.02 (0.9–1.17), *P*=0.74 (Figure 4A). In addition, *ALDH1B1*'s



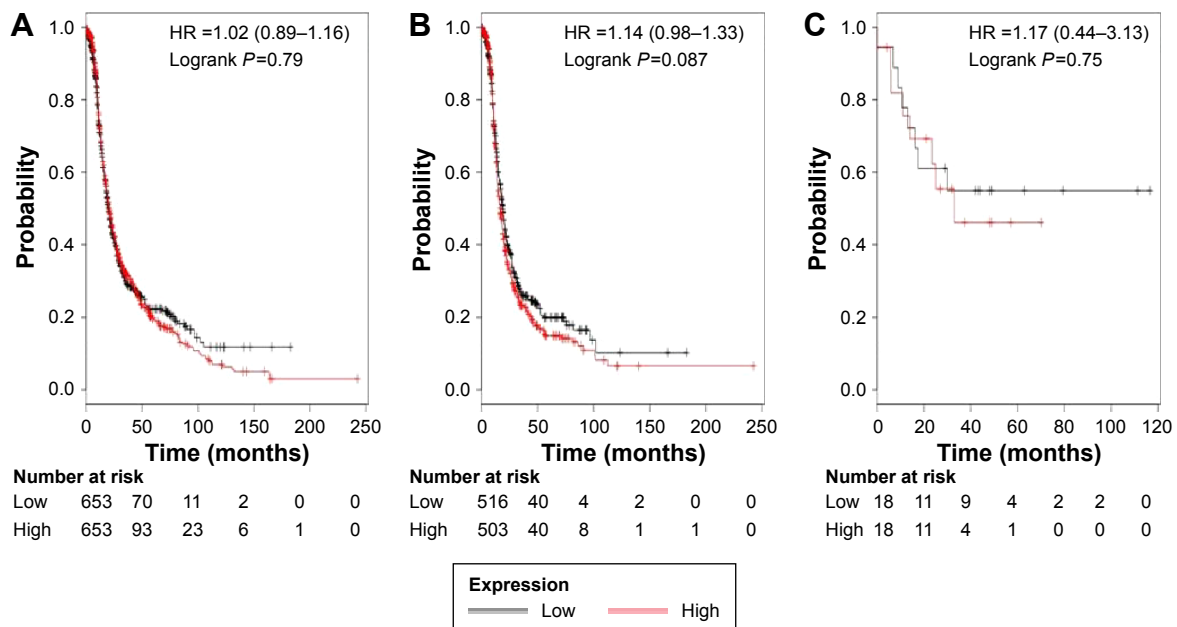
**Figure 1** The prognostic value of *ALDH1A1* expression.

**Notes:** The desired Affymetrix ID is valid: 212224\_at (*ALDH1A1*). Survival curves are plotted for (A) all patients ( $n=1,306$ ), (B) serous cancer patients ( $n=1,019$ ), and (C) endometrioid cancer patients ( $n=36$ ).

**Abbreviations:** ALDH1, aldehyde dehydrogenase I; HR, hazard ratio.

high mRNA expression was also found to be uncorrelated with OS in serous cancer patients, HR 1.11 (0.95–1.29),  $P=0.19$  (Figure 4B), and in endometrioid cancer patients, HR 1.2 (0.45–3.2),  $P=0.72$  (Figure 4C).

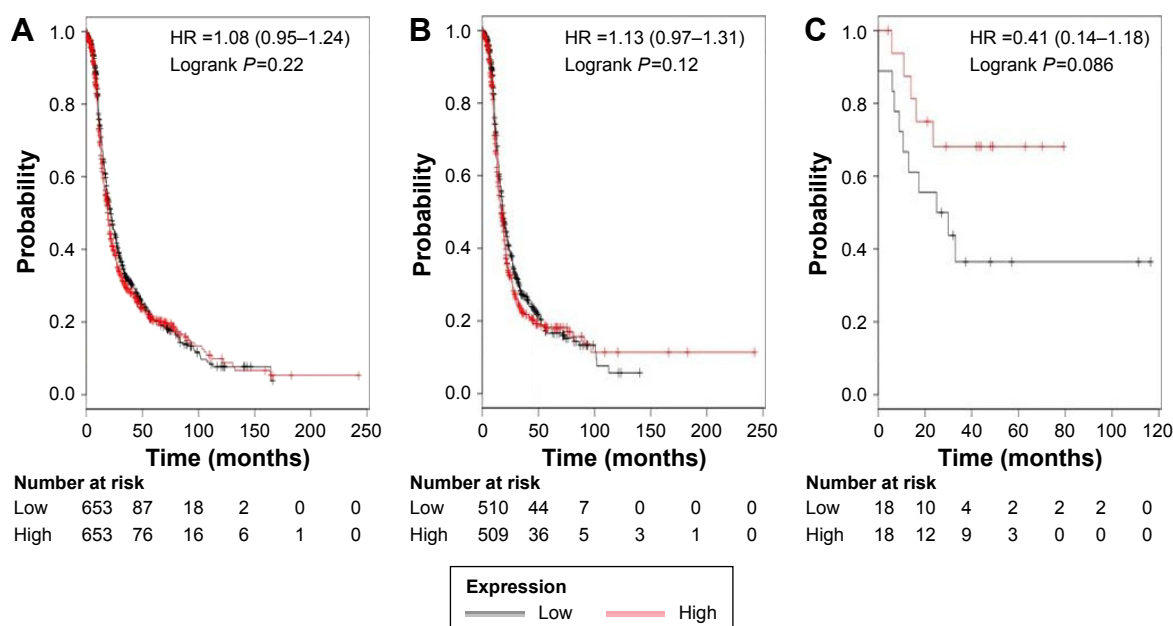
Finally, we accessed the prognostic value of *ALDH1L1*'s mRNA expression. The desired Affymetrix ID is valid: 205208\_at (*ALDH1L1*). The curves show that *ALDH1L1* expression above or below the median does not separate



**Figure 2** The prognostic value of *ALDH1A2* expression.

**Notes:** The desired Affymetrix ID is valid: 207015\_s\_at (*ALDH1A2*). Survival curves are plotted for (A) all patients ( $n=1,306$ ), (B) serous cancer patients ( $n=1,019$ ), and (C) endometrioid cancer patients ( $n=36$ ).

**Abbreviations:** ALDH1, aldehyde dehydrogenase I; HR, hazard ratio.



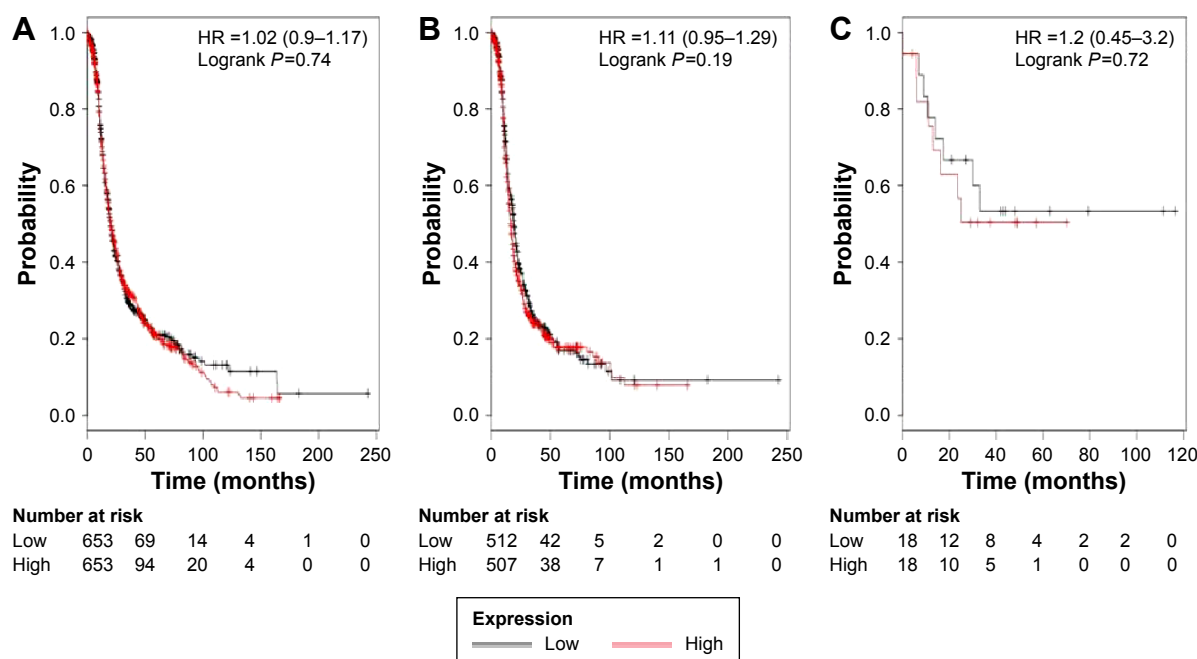
**Figure 3** The prognostic value of *ALDH1A3* expression.

**Notes:** The desired Affymetrix ID is valid: 203180\_at (*ALDH1A3*). Survival curves are plotted for (A) all patients (n=1,306), (B) serous cancer patients (n=1,019), and (C) endometrioid cancer patients (n=36).

**Abbreviations:** ALDH1, aldehyde dehydrogenase I; HR, hazard ratio.

the cases into significantly different prognostic groups in ovarian cancer patients, HR 0.91 (0.8–1.04),  $P=0.17$  (Figure 5A); serous cancer patients, HR 1.04 (0.89–1.2),  $P=0.66$  (Figure 5B); or endometrioid cancer patients, HR 0.59 (0.21–1.62),  $P=0.3$  (Figure 5C).

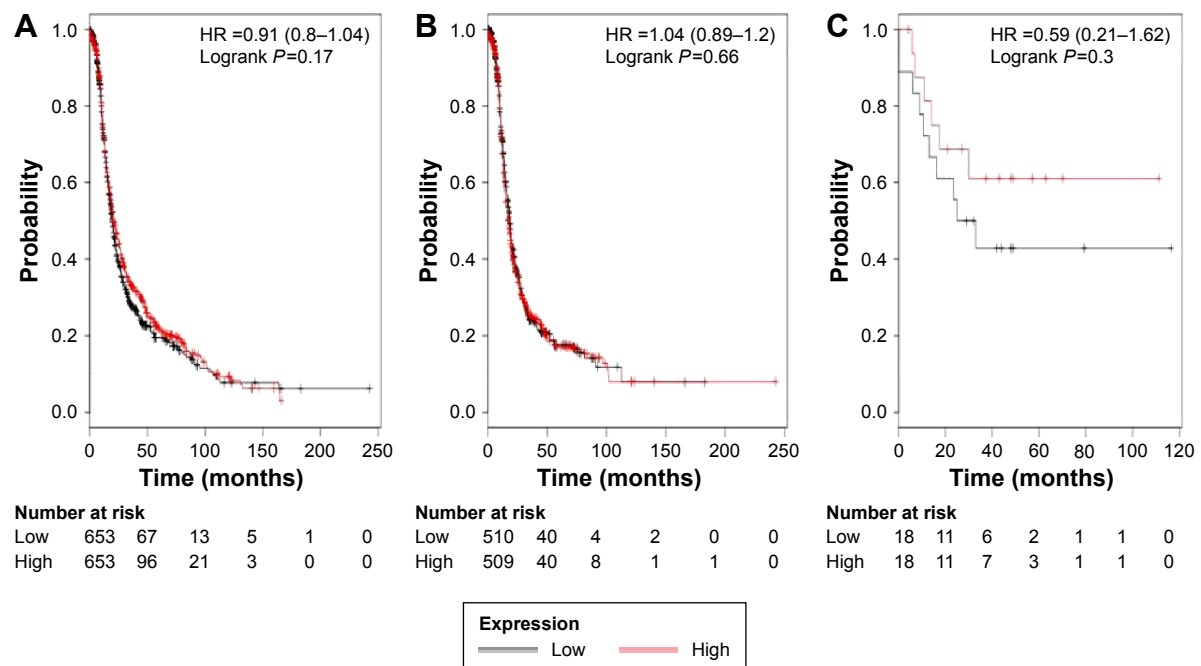
To further access the correlation of individual *ALDH1* isoenzymes with other clinicopathological features, we evaluated the correlation with pathological grades (Table 1), clinical grades (Table 2), and *TP53* mutation (Table 3) of ovarian cancer patients. As observed in Table 1, all the



**Figure 4** The prognostic value of *ALDH1B1* expression.

**Notes:** The desired Affymetrix ID is valid: 209646\_x\_at (*ALDH1B1*). Survival curves are plotted for (A) all patients (n=1,306), (B) serous cancer patients (n=1,019), and (C) endometrioid cancer patients (n=36).

**Abbreviations:** ALDH1, aldehyde dehydrogenase I; HR, hazard ratio.



**Figure 5** The prognostic value of *ALDH1I* expression.

**Notes:** The desired Affymetrix ID is valid: 205208\_at (*ALDH1I*). Survival curves are plotted for (A) all patients ( $n=1,306$ ), (B) serous cancer patients ( $n=1,019$ ), and (C) endometrioid cancer patients ( $n=36$ ).

**Abbreviations:** ALDH1, aldehyde dehydrogenase I; HR, hazard ratio.

individual *ALDH1* except *ALDH1A3* is not significantly associated with pathological grades of ovarian cancer patients. *ALDH1A3*' high mRNA expression is associated with worse OS in grade II ovarian cancer patients, HR 1.53 (1.14–2.07),  $P=0.005$ . As observed in Table 2, all the individual *ALDH1* is not significantly associated with clinical stages of ovarian

cancer patients. We find from Table 3 that *ALDH1A2*'s high mRNA expression is significantly associated with worse OS in *TP53* wild-type ovarian cancer patients, HR 2.86 (1.56–5.08),  $P=0.00036$ . In addition, *ALDH1A3*'s high mRNA expression is significantly associated with better OS in *TP53* wild-type ovarian cancer patients, HR 0.56 (0.32–1.00),  $P=0.04$ .

**Table 1** Correlation of ALDH1 isoenzymes with pathological grades of ovarian cancer patients as a result of Kaplan Mier analysis

Isoenzymes	Pathological grades	Cases	HR (95% CI)	P-value
ALDH1A1	I	37	0.8 (0.27–2.38)	0.68
	II	247	1.11 (0.82–1.49)	0.5
	III	790	0.87 (0.73–1.04)	0.12
ALDH1A2	I	37	1.55 (0.5–4.76)	0.44
	II	247	1.21 (0.9–1.63)	0.21
	III	790	1.14 (0.96–1.35)	0.14
ALDH1A3	I	37	1.17 (0.39–3.5)	0.77
	II	247	1.53 (1.14–2.07)	0.005
	III	790	1.08 (0.91–1.29)	0.37
ALDH1B1	I	37	1.69 (0.55–5.17)	0.36
	II	247	1.19 (0.88–1.6)	0.26
	III	790	1.09 (0.92–1.29)	0.33
ALDH1I1	I	37	3.28 (0.9–11.95)	0.056
	II	247	1.12 (0.83–1.51)	0.45
	III	790	1 (0.84–1.19)	0.99

**Abbreviations:** ALDH1, aldehyde dehydrogenase I; HR, hazard ratio; CI, confidence interval.

**Table 2** Correlation of ALDH1 isoenzymes with clinical stages of ovarian cancer patients as a result of Kaplan Mier analysis

Isoenzymes	Clinical stages	Cases	HR (95% CI)	P-value
ALDH1A1	I+II	126	0.59 (0.32–1.09)	0.087
	III	846	0.99 (0.84–1.16)	0.88
	IV	143	1 (0.67–1.5)	1
ALDH1A2	I+II	126	1.66 (0.9–3.07)	0.1
	III	846	1.05 (0.9–1.24)	0.54
	IV	143	1.18 (0.79–1.76)	0.43
ALDH1A3	I+II	126	0.83 (0.46–1.51)	0.55
	III	846	1.16 (0.99–1.36)	0.074
	IV	143	0.96 (0.64–1.44)	0.85
ALDH1B1	I+II	126	1.8 (0.98–3.31)	0.054
	III	846	1.02 (0.87–1.2)	0.82
	IV	143	0.87 (0.58–1.31)	0.51
ALDH1I1	I+II	126	0.73 (0.4–1.32)	0.29
	III	846	1.08 (0.92–1.27)	0.35
	IV	143	1.01 (0.68–1.52)	0.94

**Abbreviations:** ALDH1, aldehyde dehydrogenase I; HR, hazard ratio; CI, confidence interval.



**Table 3** Correlation of ALDH1 isoenzymes with *TP53* mutation status of ovarian cancer patients as a result of Kaplan Mier analysis

Isoenzymes	TP53 mutation	Cases	HR (95% CI)	P-value
ALDH1A1	No	76	0.95 (0.54–1.66)	0.85
	Yes	416	0.93 (0.73–1.04)	0.58
ALDH1A2	No	76	2.82 (1.56–5.08)	0.00036
	Yes	416	0.91 (0.71–1.17)	0.48
ALDH1A3	No	76	0.56 (0.32–1)	0.046
	Yes	416	0.98 (0.77–1.26)	0.9
ALDH1B1	No	76	0.99 (0.56–1.75)	0.99
	Yes	416	0.94 (0.74–1.21)	0.65
ALDH1L1	No	76	0.91 (0.51–1.63)	0.75
	Yes	416	0.78 (0.61–1.01)	0.055

**Abbreviations:** ALDH1, aldehyde dehydrogenase 1; HR, hazard ratio; CI, confidence interval.

## Discussion

A number of previous studies focused on the relationship between ALDH1A1 protein expression and the clinicopathologic parameters, including prognosis of tumor patients. In most types of tumors, such as lung cancer,<sup>43</sup> colorectal carcinoma,<sup>44</sup> clear cell renal cell carcinoma,<sup>45</sup> esophageal squamous cell carcinoma,<sup>46</sup> breast cancer,<sup>8,47,48</sup> gastric cancer,<sup>49</sup> head and neck cancer,<sup>50</sup> and bladder cancer,<sup>51</sup> high expression of ALDH1A1 protein was associated with tumor progression, metastasis, and poor prognosis. In contrast to the earlier studies, there were also a few reports showing that ALDH1A1 is a better prognostic marker in patients suffering from primary glioblastoma.<sup>52</sup> In an early report, Chang et al<sup>20</sup> observed that in contrast to its function in breast cancer, ALDH1A1 is a favorable prognostic factor in ovarian carcinoma. They believe that ALDH1A1, therefore, may have a different function in ovarian cancer than it does in breast cancer. However, Liebscher et al<sup>18</sup> revealed that ALDH1A1, together with epidermal growth factor receptor coexpression, is a characteristic of a highly aggressive, poor-prognosis subgroup of high-grade serous ovarian carcinoma. However, in a recent study, Huang et al<sup>15</sup> still consider that high expression of ALDH1A1 in ovarian carcinoma cells may thus portend a favorable prognosis, but its expression in tumor microenvironment may have no role in tumor behavior of ovarian carcinomas. They suggest that more studies are warranted to find out the mechanisms for this.

The prognostic role of ALDH1 isoenzyme mRNA in ovarian cancer patients was not reported. We found that five ALDH1 isoenzymes', such as *ALDH1A1*, *ALDH1A2*, *ALDH1A3*, *ALDH1B1*, and *ALDH1L1*, high mRNA expression was not to be correlated with OS for all ovarian cancer patients. In addition, all five of the ALDH1 isoenzymes'

high mRNA expression was not found to be correlated with OS in serous cancer and endometrioid cancer patients. However, *ALDH1A3*'s high mRNA expression is associated with worse OS in grade II ovarian cancer patients, HR 1.53 (1.14–2.07),  $P=0.005$ . *ALDH1A2*'s high mRNA expression is significantly associated with worse OS in *TP53* wild-type ovarian cancer patients, HR 2.86 (1.56–5.08),  $P=0.00036$ . In addition, *ALDH1A3*'s high mRNA expression is significantly associated with better OS in *TP53* wild-type ovarian cancer patients, HR 0.56 (0.32–1.00),  $P=0.04$ . ALDH1L2 is expressed in the brain, heart, liver, kidney, and pancreas tissues by using real-time polymerase chain reaction performed on an array of human tissues, and no information is available for its expression in ovarian tissues.<sup>53</sup> No survival information for ALDH1L2 in ovarian cancer patients is available, probably due to its low expression in normal ovarian tissue and ovarian cancer.

There are strong evidences showing the correlation between p53 function and ovarian cancer stem cells. Kurrey et al reported that snail and slug mediate radioresistance and chemoresistance by antagonizing p53-mediated apoptosis and acquiring a stem-like phenotype in ovarian cancer cells.<sup>54</sup> Motohara et al also observed that transient depletion of p53 followed by transduction of c-Myc and KRas converts ovarian stem-like cells into cancer stem cells.<sup>55</sup> Interestingly, ovarian cancer cells display long-term stem cell properties ex vivo and in vivo and express stem and/or progenitor cell markers, ALDH1, LGR5, LEF1, CD133, and CK6B, after inactivation of tumor suppressor genes *TP53* and *RB1*.<sup>56</sup> In our results, we find that *ALDH1A2*'s high mRNA expression is significantly associated with worse OS in *TP53* wild-type ovarian cancer patients. In contrast, *ALDH1A3*'s high mRNA expression is significantly associated with better OS in *TP53* wild-type ovarian cancer patients. The significance of correlation between p53 and individual ALDH1 isoenzymes in ovarian cancer needs further study.

ALDH1 belongs to a family of detoxifying enzymes that convert aldehydes to their corresponding carboxylic acids, and members of this family are present in many types of normal tissues.<sup>57,58</sup> Currently, the "gold standard" of the measurement of ALDH1's activity in viable cells is measured by the use of flow cytometry and fluorescent substrates for ALDH1.<sup>8,59,60</sup> It is not clear about the role of each ALDH1 isoenzyme that contributes to ALDH1 activity in ovarian cancer cells. It will be helpful to know which ALDH1 isoenzyme contributes to ALDH1 activity if we measure the changes in ALDH1 activity upon using small interfering RNAs or antibodies of individual ALDH1 isoenzymes in

ovarian cancer cells. Our current study found that unlike breast cancer, *ALDH1A1* mRNA in ovarian cancer is not associated with poor prognosis. Our current study supports that ALDH1A2 and ALDH1A3 might be major contributors to the ALDH1 activity in ovarian cancer, since *ALDH1A2* and *ALDH1A3*'s high mRNA expression was found to be significantly correlated with worse OS for some type of ovarian cancer patients. The analysis of ALDH1A1 expression will also be important for the design of treatment and the assessment of the prognosis of ovarian cancer patients by using high-quality commercial antibodies against ALDH1A1.

Please note that *ALDH1* mRNA was extracted from cancer tissues, which were composed of many type of cells, such as different types of stromal cells and epithelial cells. Thus, ALDH1 isoenzymes' mRNA expression in the individual cell types may be different. In a recent report, Isfoss et al<sup>61</sup> analyzed immunohistologically for the stem cell marker, *ALDH1A1*, in different forms of bladder neoplasia and observed that the majority of stem cell marker-positive cells were located in the connective tissue and a smaller fraction in the epithelial tissue. Stem cell marker-positive cells with nonstem cell character included stellate cells, mast cells, endothelial cells, foamy histiocytes, and neurons. Therefore, it is interesting to further study the role and clinical significance of the individual ALDH1 isoenzymes in different types of cells.

## Disclosure

The authors have no financial involvement with any organization or entity with a financial interest in the subject matter or materials discussed in the manuscript. The authors reported no conflicts of interest in this work.

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