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## Clinical Usefulness of LDH In Various Tumors – An Update

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### ABSTRACT

LDH, one of the earliest marker still being used along with troponins in the diagnosis of acute myocardial infarction is now emerging as an important marker in a wide range of cancers. Recently LDH and its isoenzymes have been extensively studied in the detection and its prognostic role in common tumors such as colorectal, breast, ovarian, prostate, liver and various other metastases. LDH levels have been correlated with CEA, CA 15.3, CA 125, CA19.9 and Hodgkin's lymphomas. Further, isoenzymes of LDH are being studied extensively and each isoenzyme was found to be specific for a particular cancer. LDH has been linked to intracellular enzymes through damaged cells in apoptosis and deregulation. Studies suggest that inhibiting LDH activity may lead to possible anticancer treatment. The objective of this review article is to present the outcome of various research findings during the last two decades and to make awareness among research scholars to undertake further research to establish the exact clinical role of LDH in each type of cancer.

**Keywords:** Tumor, LDH, CEA, CA 125, HCC, CA 15.3

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## INTRODUCTION

The new directions in the investigation of Lactate Dehydrogenase (LDH) as a marker are based on the principle that tumor cells release intracellular enzymes through damaged cell membrane, due to intracellular mitochondrial machinery alteration, and apoptosis deregulation. Intracellular LDH activity in different cell line and tumor tissues obtained from patients, will enable in understanding the complexity in cancer biochemistry but also in early clinical diagnosis. Based on understandings of the LDH altered metabolism, new therapy option is created with aims to blocking certain metabolic pathways and to stop tumors growth.<sup>1</sup> The deviation to H subunit of LDH isoenzymes was seen in certain cases of germ cell tumor, while deviation to M subunit was noted in epithelial and metastatic tumor patients. Each parameter is useful as a tumor marker for the specific histological type of ovarian tumor; CA125 for non-mucinous epithelial carcinoma, CEA for mucinous tumor and Krukenberg tumor, AFP for yolk sac tumor, LDH and LDH isoenzymes for dysgerminoma and other solid germ cell tumors. In addition, preoperative diagnosis of histological types of ovarian tumors may be possible by combining these tumor markers.<sup>2</sup>

Elevation of LDH isoenzymes (LD-1) has been found to be specific to testicular cancer among all neoplasms.<sup>3</sup> Studies suggest that high level of serum LDH is associated with poor overall survival in several malignancies, but its link to cancer-specific survival is unclear. Site-specific analysis showed high LDH to correlate with an increased risk of death from prostate, pulmonary, colorectal, gastro-oesophageal, gynaecological and haematological cancers. Serum LDH assessed within intervals closer to diagnosis was more strongly associated with overall and cancer-specific death. There is an inverse association of baseline serum LDH with cancer-specific survival, corroborating its role in cancer progression.<sup>4</sup> The validity of LDH were sensitivity 57.1%, specificity 84.1%, accuracy 78.7%, positive predictive values 47.1% and negative predictive values 88.8% for malignancy of ovarian tumour. The validity of CA-125 were sensitivity 78.6%, specificity 82.3%, accuracy 81.6%, positive predictive values 52.4% and negative predictive values 93.9% for malignancy of ovarian tumour with the validity of LDH and serum CA-125 level (combined, i.e. both positive).<sup>5</sup>

Several factors, including over expression of LDH and monocarboxylate transporters (MCTs), promote an aerobic lactate production that allows some cancer cells to sustain higher proliferation rates in hostile environments outside the cell. Metabolically altered tumours from the trained animals exhibited lower values for lactate concentration than the control group. The decreased lactate concentration was associated with a shift in the tumour LDH isozyme profile towards LDH-1.<sup>6</sup> Data from several analyses on different tumour types

seem to suggest that LDH levels may be a significant prognostic factor and role of LDH in Hepatocellular carcinoma (HCC) has been investigated by different authors in heterogeneous populations of patients. It has been tested as a potential biomarker in retrospective, small, and nonfocused studies in patients undergoing surgery, transarterial chemoembolization (TACE), and systemic therapy. In the major part of these studies, high LDH serum levels seem to predict a poor outcome.<sup>7</sup>

The availability of inhibitors with drug-like properties will allow the evaluation in the near future of the real potential of LDH inhibition in anticancer treatment, also making the identification of the most responsive neoplastic conditions possible.<sup>8</sup> Using a specific small molecule LDH-A inhibitor it has been demonstrated that LDH-A is essential for cancer-initiating cell survival and proliferation. Thus, LDH-A can be a viable therapeutic target for Non Small Cell Lung Cancer (NSCLC), including cancer stem cell-dependent drug-resistant tumors.<sup>9</sup> Cytochemical stain ability for LDH-M subunits corresponded well to the results of LDH zymogram, confirming that the LDH stain with urea treatment is a useful method for detecting malignancy in cytological specimens.<sup>10</sup>

Serum LDH is a non-specific marker for lymphoma whose prognostic significance is well established for both indolent and aggressive lymphomas at the time of diagnosis. The performance characteristics of this enzyme in predicting relapse in patients with diffuse large B-cell lymphoma has not been well studied. The likelihood ratio of relapse was 4.65 for patients who had 1.5-fold increases in serum LDH above baseline. The sensitivity, specificity, positive and negative predictive values of 1.5-fold increases for detecting relapse, compared to clinical and imaging findings were 0.18, 0.95, 0.55, and 0.79, respectively. A 1.5-fold increase in serum LDH, over a period of 3 months, is associated with increased likelihood of relapse from diffuse large B-cell lymphoma.<sup>11</sup> Patients with higher clinical TNM staging were having higher serum LDH levels. The serum LDH levels at sixth months following surgery showed a trend of statistically significant difference between patients with and without adverse events as increased serum LDH levels in breast cancer patients shows poor prognosis, surgical outcome or advanced metastases. Serum LDH monitoring can be used as a prognostic biomarker in patients of breast cancer. More studies on larger sample size and long-term follow-up in patients specifically with higher serum LDH levels.<sup>12</sup>

Suppressing LDH-A increased EO9-induced DNA damage in p53+/+ cancer cells, but importantly had no additive effect in non-cancer cells.<sup>13</sup> Multivariate Cox proportional hazard analysis of these three items showed a statistically significant difference in LDH level and Gleason score 9 +/- 10 ( $p = 0.0167$  and  $0.0371$ ). LDH was suggested to be an excellent prognostic indicator, because of its objectivity and convenience of measurement, in prostate

cancer patients with bone metastasis.<sup>14</sup> Cancer cells produce a substantial amount of energy through aerobic glycolysis even in the presence of adequate oxygen. LDH, a key regulator of glycolysis, reversibly catalyzes the conversion of pyruvate to lactate. Recently, oxamate, an inhibitor of LDH, has been shown to be a promising anticancer agent. However, the detailed mechanism remains largely unclear.<sup>15</sup>

It was found that tumor LDH affinity in forward reaction was the same as normal LDH but  $V_{max}$  of cancerous LDH was higher relative to normal LDH. In reverse reaction, affinity of tumor LDH for lactate and NAD(+) was lower than normal LDH, also enzyme efficiency for lactate and NAD(+) was higher in normal samples. The  $E_a$  of reverse reaction was higher in cancerous tissues, and hence low LDH affinity for lactate and NAD(+) is a valuable tool for preserving lactate by cancer cells. Increasing of LDH affinity may be a valid molecular target to abolish lactate dependent tumor growth and kinetic characteristics of LDH could be a novel diagnostic parameter for human breast cancer.<sup>16</sup> LDH is receiving a great deal of attention as a potential diagnostic marker or a predictive biomarker for many types of cancer and as a therapeutic target for new anticancer treatments.<sup>17</sup>

A high serum LDH level is associated with a poor survival in solid tumors, in particular melanoma, prostate and renal cell carcinomas, and can be used as a useful and inexpensive prognostic biomarker in metastatic carcinomas.<sup>18</sup> The prognostic value of LDH levels in the prognosis of colorectal cancer patients has been assessed for years, although the results remain controversial and heterogeneous. High LDH levels are associated with poor Oxidative Stress (OS) among colorectal cancer patients, although these levels are not significant predictors of PFS.<sup>19</sup> Overall survival of cancer patients with serum LDH greater than 1000 IU/L. is a well-known poor prognostic factor in patients with malignancies. , serum LDH level > 1000 IU/L predicted a terminal stage in metastatic cancer patients. OS was significantly prolonged in patients indicated for effective palliative treatment and LDH level decreased to normal at 2 months.<sup>20</sup>

Application of LDH-5 increased the sensitivity of Non-Hodgkin's lymphoma (NHL) detection, identifying 53.4% of NHL patients as positive, compared with the measurement of total LDH levels (36.5% sensitivity). LDH-5 concentrations increased with clinical stage, extra-nodal site involvement, and performance status of patients with NHL. Exposure to a hypoxic environment induced the expression of LDH-5 and its overexpression correlated with HIF1 $\alpha$  cytoplasmic accumulation in NHL cells. In multivariate analyses, LDH-5 was an independent marker for progression-free survival in patients with NHL. Overall, the expression of LDH-5 was elevated in NHL, showing an association with tumor hypoxia and unfavorable prognosis. Thus, LDH-5 emerges as a promising prognostic predictor for NHL

patients.<sup>21</sup> Patients with normal serum levels of all tumor markers had better outcome than others and those with normal serum LDH and CEA levels (whatever CA19-9) levels had associated with better survival compared with other possible alternatives. Serum levels of LDH, CEA, and CA19-9 had significant affect on survival in Metastatic Pancreatic Cancer (MPC) patients.<sup>22</sup>

The serum levels of LDH, Tissue Polypeptide Specific Antigen (TPS), Carcino Embryonic Antigen (CEA) and beta2-MG in the patients in a stable or progressive phase did had no significant changes after chemotherapy ( $P>0.05$ ). Combined detection of LDH, TPS, CEA and beta2-MG can be helpful to assist diagnosis of NHL and treatment evaluation.<sup>23</sup> Aqueous humor and plasma examination revealed elevated ratios LDH and phosphoglucoseisomerase (PGI). Furthermore, subretinal fluid examination demonstrated concentrations of LDH and PGI higher than aqueous humor.<sup>24</sup>

LDH activity in cancer tissue was very high and its gradual decrease in normal tissue surrounding tumor with the distance from carcinoma was recognized. LDH isozyme ratio ( $LDH4 + LDH5/LDH1 + LDH2$ ) and H subunit % ( $LDH1 + 3/4LDH2 + 1/2LDH5 + 1/4LDH$ ) in cancer tissue were obviously different from those of control materials, LDH isozyme ratio in normal tissue within 4 cm from the edge of carcinoma and H subunit % within 6 cm showed the significant difference to those in control materials. The increase of tissue CEA content, LDH activity and the deviation of LDH isozymatic pattern in normal tissue could be early signs of malignancy before the morphologic changes.<sup>25</sup> Variations in metastasis with smoking in Pre- and post -treatment levels were statistically compared and the role of surgery, radiotherapy and chemotherapy compared.<sup>26</sup> Higher serum concentration of CA15.3 and LDH was associated with regional and distant metastases. There was a significantly higher serum CA15.3 concentration in animals with lymph node metastasis when compared with animals without metastasis. There were no significant differences in CEA among groups. Expression of CA15.3 and CEA in canine serum was confirmed by Western blotting. Serum CA15.3 can be used to distinguish nonmetastatic from metastatic carcinomas.<sup>27</sup>

Early diagnosis of liver metastasis is of great significance. The sensitivity and specificity of combined tumor and biochemical markers are rather good in screening colorectal liver metastasis.<sup>28</sup> The correlation of the tumor markers CEA, CA 19-9, and the serum marker CRP with radiological imaging in patients with mCRC receiving first-line chemotherapy. Further data analyses would be helpful to develop a predictive model for tumor response based on an early tumor marker increase or decrease.<sup>29</sup> Within multivariate analyses, pre-treatment log [CA 19-9] (as continuous variable for TTP) and log [bilirubin] as well as log

[CRP] (for OS) had an independent prognostic value. A CA 19-9 decline of  $\geq 25\%$  during the first two chemotherapy cycles was predictive for TTP and OS, independent of the applied CA 19-9 assay. Baseline CA 19-9 and CA 19-9 kinetics during first-line chemotherapy are prognostic in advanced PC. Besides that finding other serum markers like CRP, LDH and bilirubin can also provide prognostic information on TTP and OS.<sup>30</sup>

The median PFS of patients receiving bevacizumab or not was significantly different in the high LDH level group (9.9 and 6.9 months, respectively). The addition of bevacizumab in the first-line treatment setting could improve the PFS of mCRC patients notably. However, the benefit could only be potentially reflected on patients with high serum LDH level.<sup>31</sup> A pretreatment value and at least one serial measurement during the first two cycles of second-line chemotherapy for CA 19-9, CEA, CRP, and LDH had to be available in order to evaluate the prognostic role of kinetics on overall survival. A cutoff of a  $>20\%$  increase from baseline during treatment was defined in order to form groups with suspected different outcomes.<sup>32</sup>

Among the individual laboratory tests performed, CEA elevation heralds liver metastases significantly more frequently. LDH is the liver function test most frequently elevated when liver metastases are first suspected. When CEA is directly compared with a battery of LFTs, CEA is statistically significantly more frequently elevated. In fact, suspicion of liver metastases would have been delayed by the omission of LFTs in only 2.2 percent of patients. Therefore, LFTs should be deleted from the follow-up of colorectal cancer patients, decreasing costs without significantly decreasing accuracy.<sup>33</sup> Serum ferritin was low in 60% of anemia patients and CEA and LDH were elevated in 45% and 46% of patients with colorectal cancer. Iron deficiency anemia is a common clinical manifestation of patients with colorectal carcinoma, and occurred more frequently in females, patients with right colon tumor and with larger tumor size.<sup>34</sup> ESR, LDH, CEA, haptoglobin, fibrinogen, CH50, Bc-globulin (C3), B1E-globulin (C4), T-cell, B-cell and phytohemagglutinin (PHA) in patients with renal cell carcinoma, showed positive rates of ESR, LDH, CEA, haptoglobin, fibrinogen, CH50, C3, C4, T-cell, B-cell and PHA.<sup>35</sup>

HCC remains one of the most important malignancies in Japan and LDH exists in various types of human tissue and neoplasms, has also been reported to demonstrate a high level (especially LDH 5) in the serum of patients with HCC, the portion of poorly differentiated HCC stained positively for it. It was thus speculated that LDH was mainly produced in the portion of undifferentiated HCC. In addition the undifferentiated HCC were strongly positive for Ki-67, while, in contrast, the poorly HCC was only weakly positive for Ki-67, and hence HCC with a high serum level of LDH appears to show both a rapid growth and highly malignant tumors.<sup>36</sup>



LDH is of some value in the follow-up of marker-negative patients and can indicate a persistent tumour or a recurrence. Some authors have found evidence that initially elevated LDH may be an independent prognostic factor. The isoenzyme LDH 1 is easily determined, shows elevated levels in the presence of testicular germ cell tumours even if the total LDH is normal and is possibly more specific. However, the data presently available cannot yet justify its general application.<sup>37</sup> For follow-up, AFP, hCG and LDH should be evaluated for advanced TGCT and clinical stage I nonseminomas, whereas clinical stage I seminomas should be monitored without any markers.<sup>38</sup> Preoperative serum LDH has been used as a prognostic indicator for patients with HCC treated with sorafenib or undergoing transcatheter arterial chemoembolization, but its significance in predicting survival of HCC patients who received curative resection remains undefined.. The prognostic significance of preoperative serum LDH was determined by Kaplan-Meier analysis and a Cox proportional hazards regression model. The association between the preoperative serum LDH and clinicopathological parameters was evaluated by the  $\chi^2$  test or linear regression analysis when appropriate. Higher preoperative serum LDH level was associated with worse prognosis. In a multivariate Cox proportional hazards analysis, the preoperative serum LDH level could predict overall survival and recurrence independently.

Higher preoperative serum LDH level was associated with worse prognosis. In a multivariate Cox proportional hazards analysis, the preoperative serum LDH level could predict overall survival and recurrence independently. Higher preoperative serum LDH level is associated with the elevated serum AFP, the presence of HbsAg, larger tumor size, the presence of macrovascular invasion, the advanced tumor-lymph node-metastasis stage, worse tumor differentiation, and Child-Pugh B. Preoperative serum LDH level was an inexpensive, simple, convenient, and routinely measured biomarker exhibiting a potential to select patients at high risk with poor clinical outcome for appropriate treatment strategies.<sup>39</sup>

Tumor tissue from a testicular germ cell tumor transplanted into athymic mice had a high activity of LDH-1. There was a good correlation between S-LDH-1 and tumor volume. S-LDH may be used as a tumor marker in patients with testicular germ cell tumors in addition to other diagnostic tests. In patients with a history of testicular germ cell tumors and an unexplained elevation of S-LDH, raised S-LDH-1 may indicate the presence, and normal S-LDH-1 the absence, of testicular germ cell tumors.<sup>40</sup> Regarding survival, S-LDH-1 and an estimate of total tumour mass had most impact with additional information from S-hCG only. S-LDH-1 may be used as a tumour marker in addition to S-hCG and S-AFP in patients with metastatic testicular germ cell tumour.<sup>41</sup> LDH-5 isoenzyme was strongly expressed in cancer cells, exhibiting a mixed cytoplasmic/nuclear subcellular pattern. Interestingly, a high

LDH-5 content in tissue sections was not invariably accompanied by high LDH serum levels. High HIF1alpha tissue expression was linked to high tissue LDH-5 expression. Serum and tissue LDH is up-regulated in gynaecologic and breast malignancies and in a subset of benign conditions such as fibro- and cystadenomas. The release of LDH, however, in the blood stream is partly related to the LDHA gene up-regulation.<sup>42</sup>

Previous reports have suggested that a high serum cyclosporine A (CsA) level could result in a lower incidence of acute-graft-versus-host disease (aGVHD). An elevated LDH level has been reported to be an adverse predictor of outcome in stem cell transplantation (SCT) for acute myeloid leukemia. A retrospectively analyzed records of 24 patients who received allogeneic SCT from an HLA-matched sibling donor for acute and chronic myelogenous leukemia. Univariate analysis showed that two factors (the serum CsA level at the third week after SCT and the LDH level at the third week after SCT) were significantly associated with the incidence of aGVHD among several variables (age, sex, stem cell source, cell dose, C-reactive protein, absolute lymphocyte count, conditioning regimens, and time to engraftment). A higher serum level of CsA and lower serum LDH level at the third week after SCT were associated with a lower incidence of aGVHD ( $P=0.015$ ,  $0.030$ ). In multivariate analysis, the serum CsA level (hazard ratio [HR], 0.12; 95% confidence interval [CI], 0.022-0.652,  $P=0.0014$ ) and serum LDH level (HR, 6.59; 95% CI, 1.197-36.316,  $P=0.030$ ) at the third week after SCT were found to be independent factors that were significantly associated with the development of aGVHD. Suggesting that a high CsA level and low LDH level might predict a low cumulative incidence of aGVHD after allogeneic transplantation from a matched sibling donor.

LDH level at the third week after SCT were significantly associated with the incidence of Graft- Versus-Host-Diseases (GVHD) among several variables (age, sex, stem cell source, cell dose, C-reactive protein, absolute lymphocyte count, conditioning regimens, and time to engraftment). A higher serum level of Cyclosporine (CsA) and lower serum LDH level at the third week after Stem Cell transplantation (SCT) were associated with a lower incidence of aGVHD. A high CsA level and low LDH level might predict a low cumulative incidence of aGVHD after allogeneic transplantation from a matched sibling donor.<sup>43</sup> This experiment was conducted to study variations of serum testosterone and seminal characteristics of Markhoz male goats. Blood samples were obtained via jugular vein, and semen was collected by using an artificial vagina from 14 fertile male goats (2–3 years of age), at 15-day intervals starting on 15 July and ending on 30 October 2010 (during breeding and non-breeding season). Semen volume, total sperm (volume× concentration), live sperm (%), abnormal sperm (%) and semen pH were significantly superior during the late summer and early



autumn (breeding season). Variation of sperm density, motility and progressive motility was not significant during the sampling period. The results presented show that the lowest and highest levels of lactate dehydrogenase in the seminal plasma were recorded in late October (2.82 U/ml) and in late August (4.81 U/ml), respectively. Moreover, the study indicated that the serum testosterone concentration was higher during late summer and early autumn ( $p < 0.05$ ) than at any other of sampling period. There were negative correlations between volume and sperm density ( $-0.135$ ,  $p < 0.05$ ), and positive correlations between volume and percentage live sperm (0.224) and percentage progressive motility (0.194,  $p < 0.01$ ). Sperm density was correlated with live sperm (0.200,  $p < 0.05$ ) and progressive motility (0.202,  $p < 0.01$ ). The correlation between live sperm and progressive motility was 0.554 ( $p < 0.01$ ). Furthermore, the results in this study indicated a significant positive correlation between live sperm and LDH (0.450) and a negative correlation between sperm density and LDH concentration ( $-0.272$ ) ( $p < 0.01$ ). Significant, but positive correlations were found between sperm motility and LDH (0.542) and testosterone concentration (0.522), respectively ( $p < 0.05$ ). In conclusion, this study demonstrated that the best obtained semen was collected in late summer (during decreasing photoperiod) and early autumn (September and October). This also coincides with the natural breeding season of Markhoz goats in Iran.

A significant positive correlation between live sperm and LDH and a negative correlation between sperm density and LDH concentration, was observed. Significant, but positive correlations were found between sperm motility and LDH and testosterone concentration, respectively. The best obtained semen was collected in late summer (during decreasing photoperiod) and early autumn (September and October). This also coincides with the natural breeding season of Markhoz goats in Iran.<sup>44</sup>

Comparing the histological types of ovarian cancer, serous cystadenocarcinoma presented higher peritoneal fluid LDH levels than endometrioid or mucinous cystadenocarcinoma. No difference in peritoneal fluid LDH was observed comparing different stages of ovarian cancer. Fluid LDH may be an efficient biochemical marker in diagnosis of ovarian cancer.<sup>45</sup> LDH, HBDH, TPA and CA125 were correlated with the clinical stage while CEA, CA19-9 and STN did not show any correlation. From analyses of tumor marker levels according to histologic types, all patients with a ratio of CA125 to CEA of  $>1,000$  had serous cystadenocarcinoma and a ratio of CA125 to CA19-9 of  $>50$  showed serous cystadenocarcinoma or endometrioid adenocarcinoma.<sup>46</sup>

Elevated levels of CA 125 and LDH were found to predict decreased survival. Initial measurement of CA125 may, therefore, provide valuable prognostic information.<sup>47</sup> Multiple Cox regression analysis showed that international Prognostic Index (IPI) score complemented

by the additional serum markers beta2-M and CA125 was a better prognosticator of overall and event-free survival than LDH alone. This result suggests that if the combination of three elevated serum tumor markers.<sup>48</sup>

Diagnostic indices of LDH, GGT, and CA153 were 174 U/L, 32 U/L, and 26.48 µg/L, respectively. The areas under the curves of LDH, GGT, and CEA were 0.795, 0.784, and 0.661, respectively, and sensitivities of parallel tests for LDH and CA153 and for GGT and CA153 were 88.6% and 85.7%, respectively. The specificity of serial tests for both pairs of enzymes was 97.7%. The sensitivity and specificity of combined tumor and biochemical markers could be used as indicators during screening for breast-liver metastasis.<sup>49</sup> LDH had the highest predictive value for failure to achieve complete remission. A shorter OS was associated with increased LDH, beta2-M and CA 125 whereas CA 15.3 was associated with a shorter EFS. When elevated at diagnosis, CA 125 and CA 15.3 should be monitored during follow-up of patients with NHL.<sup>50</sup> A rapid increase in the ALT-LDH index in conservative survivors but not in fatal patients. While the prognostic sensitivity and specificity of the ALT-LDH index was low on admission, at day 3 they were superior to the results of MELD. ALT-LDH index was useful to predict the prognosis of the patients with acute liver injury and should be helpful to begin preparation for LT soon after admission.<sup>51</sup>

MI though the mechanism involved in acute liver failure (ALF) has not yet been clarified, microcirculatory disturbance in the liver appears to play a pivotal role in the progression of this disease. To confirm the existence of hepatic hypoxic conditions, we evaluated the amounts of LDH in hepatocytes, since its production increases under low oxygen concentrations. Histological examination was performed in 7 patients with ALF. All 7 patients underwent a liver biopsy during the acute phase of ALF, and 4 of them underwent a second biopsy during the recovery phase. The obtained samples were immunohistochemically stained with anti-LDH5 and anti-CD-68 antibodies. As controls, Samples were examined from patients with acute hepatitis, chronic hepatitis and liver cirrhosis. The production of LDH by hepatocytes and the number of CD-68 positive macrophages were markedly increased at the acute phase of ALF, and both of these effects abruptly decreased during the recovery phase. By contrast, most of the samples from the patients with chronic hepatitis and acute hepatitis showed slightly any increase in LDH staining. In cirrhotic patients, partially elevated LDH production was observed mainly around the central vein, but the staining intensity was less compared to that in ALF patients. These findings indicate that hepatic hypoxic conditions exist in ALF at the acute phase and seem to closely correlate with macrophage over activation in the liver. We giving specifications microcirculatory disturbance may be a key process in the development and progression of ALF<sup>52</sup>.

Most of the samples from the patients with chronic hepatitis and acute hepatitis showed slightly any increase in LDH staining.

LDH and its isoenzymes should be determined in every patient with suspected liver metastatic disease. The isomorphic pattern of LDH isoenzymes is apparently associated with higher values for total LDH and was common among the patients with multiple metastatic sites<sup>53</sup>. Ascites is the pathologic accumulation of fluid within the peritoneal cavity. Because many diseases can cause ascites, in particular cirrhosis, samples of ascitic fluid are commonly analyzed in order to develop a differential diagnosis. The concept of transudate versus exudate, as determined by total protein measurements, is outdated and the use of serum-ascites albumin gradient as an indicator of portal hypertension is more accurate. LDH, VEGF, and other tumor markers can be helpful in distinguishing between malignant and benign conditions. Glucose and adenosine deaminase levels may support a diagnosis of tuberculous disease, and amylase level may indicate a diagnosis of pancreatitis.

LDH- VEGF, and other tumor markers can be helpful in distinguishing between malignant and benign conditions. Glucose and adenosine deaminase levels may support a diagnosis of tuberculous disease, and amylase level may indicate a diagnosis of pancreatitis. Given the specificity and sensitivity of laboratory results, accurate diagnosis should be based on both laboratory data and clinical judgment.<sup>54</sup> No significant LDH release was seen with control lymphocytes of normal persons or with lymphocytes from patients with alcoholic cirrhosis. Lymphocyte-mediated liver cell damage "in vitro" occurs in both primary biliary cirrhosis and chronic active liver disease.<sup>55</sup>

Serum LDH levels could be a prognostic factor for sorafenib-treated patients with several types of solid tumor because it reflects hypoxic circumstances in aggressive tumors. For HCC, however, the prognostic role of LDH has been controversial. serum LDH levels in HCC patients were affected by liver fibrosis but not by the tumor stage, and these LDH levels could be a marker for early response to sorafenib. A marked increase in serum LDH levels during sorafenib administration might also indicate subsequent acute liver failure. Close observation of serum LDH levels before and during sorafenib treatment could be useful in managing treatment of patients receiving this therapy.<sup>56</sup> HCC is the most common primary liver tumour (80–90%) and represents more than 5.7% of all cancers. Although in recent years the therapeutic options for these patients have increased, clinical results are yet unsatisfactory and the prognosis remains dismal. Clinical or molecular criteria allowing a more accurate selection of patients are in fact largely lacking. LDH is a glycolytic key enzyme in the conversion of pyruvate to lactate under anaerobic conditions. In preclinical models, upregulation of LDH has been suggested to ensure both an efficient

anaerobic/glycolytic metabolism and a reduced dependence on oxygen under hypoxic conditions in tumour cells. Data from several analyses on different tumour types seem to suggest that LDH levels may be a significant prognostic factor. The role of LDH in HCC has been investigated by different authors in heterogeneous populations of patients. It has been tested as a potential biomarker in retrospective, small, and nonfocused studies in patients undergoing surgery, transarterial chemoembolization (TACE), and systemic therapy. In the major part of these studies, high LDH serum levels seem to predict a poorer outcome..

The role of LDH in HCC has been investigated by different authors in heterogeneous populations of patients. It has been tested as a potential biomarker in retrospective, small, and nonfocused studies in patients undergoing surgery, TACE, and systemic therapy.<sup>57</sup>

Activities of LDH, GDH, AST, and ALT, but not CK, were significantly higher in UCD-003 than in normal hens. A bimodal distribution of activities of all enzymes was found in the UCD-003 hens, with some birds showing activities comparable with those of the normal hens and others with values that were 2-10 times greater than those found in normal hens. that measurement of enzyme activities indicative of liver damage in birds, particularly AST, LDH, and GDH, is a valuable tool in the diagnosis of fatty liver-hemorrhagic syndrome in a flock of layers.<sup>58</sup> The mean values of LDH 1 through LDH 5 in the livers of normal cows were 31.7, 24.8, 27.3, 12.8, and 3.3%, respectively. In cases with hydropic degeneration of the liver, the patterns revealed increases of LDH 1 and LDH 2 as compared to normal cows. The patterns showed a decrease of LDH 1 and an increase of LDH 2 in fatty change of the liver. Congestion of the liver alone decreased LDH 1 and increased LDH 3, LDH 4 and LDH 5. Necrosis of the liver decreased LDH 1 and LDH 2, and increased LDH 3, LDH 4 and LDH 5. It was suggested that the functional hepatocellular damage due to anoxia might be a important factor of the change of liver LDH isoenzyme patterns.<sup>59</sup>

Serum LDH level can serve as a biochemical tool in assessing the malignant potential of premalignant lesions. Estimation of serum LDH may be used to screen the cases of oral malignancy as an adjunct to diagnosis.<sup>60</sup>

The elevation of the LDH serum level correlated to the Invasive status, metastatic status and poor outcome, while that of the serum  $\beta$ -hCG level correlated only to the metastatic status. Immunohistochemical expression of  $\beta$ -hCG was observed in syncytiotrophoblastic giant cells in 11 tumors and a few mononuclear seminoma cells In 36 tumors. Expression was not associated with the malignancy potential, except where the expression In mononuclear cells Inversely correlated to the invasive status. Most seminomas produce a slight amount of hCG; that an elevated hCG serum level Indicates the presence of metastatic tumors and mainly reflects an increase in tumor volume but not in cellular malignancy potential; and that the

LDH serum level, rather than hCG, is more useful as a prognostic indicator for patients with seminoma.<sup>61</sup> Each of CA 125, CEA, AFP, LDH and its isoenzymes are useful as a tumor marker for the specific histological type of ovarian tumor; CA125 for non-mucinous epithelial carcinoma, CEA for mucinous tumor and Krukenberg tumor, AFP for yolk sac tumor, LDH and LDH isoenzymes for dysgerminoma and other solid germ cell tumors. In addition, preoperative diagnosis of histological types of ovarian tumors may be possible by combining these tumor markers.<sup>62</sup>

Serum biomarkers predicting prognosis have not been adequately explored in HCC patients. Elevated serum CEA level was a risk factor related to poor HCC overall survival and advanced BCLC staging contributed to a lower overall survival in HCC patients. HCC could benefit from surgical resection, TACE, and radiotherapy. ROC curves demonstrated that different from CEA, elevated GGT and LDH could accurately predict HCC overall survival. Serum GGT and LDH together with higher BCLC staging should be potential predictive factors for HCC overall survival.<sup>63</sup> HCC is the most common primary liver tumour (80-90%) and represents more than 5.7% of all cancers. Although in recent years the therapeutic options for these patients have increased, clinical results are yet unsatisfactory and the prognosis remains dismal. Clinical or molecular criteria allowing a more accurate selection of patients are in fact largely lacking. The role of LDH in HCC has been investigated by different authors in heterogeneous populations of patients. It has been tested as a potential biomarker in retrospective, small, and nonfocused studies in patients undergoing surgery, transarterial chemoembolization (TACE), and systemic therapy. In the major part of these studies, high LDH serum levels seem to predict a poorer outcome.<sup>64</sup>

In many different species, LDH constitutes a major checkpoint of anaerobic glycolysis, by catalyzing the reduction of pyruvate into lactate. This enzyme has recently received a great deal of attention since it may constitute a valid therapeutic target for diseases so different as malaria and cancer most invasive tumour phenotypes show a metabolic switch (Warburg effect) from oxidative phosphorylation to an increased anaerobic glycolysis, by promoting an upregulation of the human isoform-5 of LDH, which is normally present in muscles and in the liver. Hence, inhibition of hLDH-5 may constitute an efficient way to interfere with tumour growth and invasiveness.<sup>65</sup>

## CONCLUSION

This review article has brought out the clinical usefulness of measuring LDH and its role in tumor detection and prognostic evaluation. The usefulness of its isoenzymes have been found to be very useful in the initial diagnosis and later in the prognosis of testicular, dysgerminoma, and solid cell tumors. Its usefulness has been also highlighted in overall

survival evolution in many neoplasms. Its prognostic usefulness has also been found in colorectal, prostate, gynaecological and haematological cancers. Elevated LDH levels have been observed in all invasive metastatic and poor outcome of various cancer treatments. The potential use for LDH inhibition as a tool for anticancer treatment has also been highlighted. LDH is a simple test, could be easily done in any clinical laboratory with minimum resource and hence could serve as a routine diagnostic supportive test along with tumor markers such as CEA, CA 125, CA 15.3 and CA 19.9 in the detection and prognostic outcome. Further research is needed in this direction to firmly establish LDH as a tumor marker for various cancers.

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