کارگاه‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

آموزش مهارت های کاربردی در تدوین و چاپ مقاله
Systematic Review: Endocrine Abnormalities in Patients with Liver Cirrhosis

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Abstract

Background: Cirrhosis is the end stage of many different forms of acute and chronic liver damages. Interactions between liver and endocrine system is significant, because liver is the main organ of metabolism and catabolism of many proteins.

Aim: In this study, current literature about endocrine abnormalities among patients with liver cirrhosis was reviewed.

Methods: A PubMed search was performed on English literature from January 1990 onward to find human studies reporting endocrine dysfunction in liver cirrhosis. Relevant articles were included and reviewed by two expert reviewers. Data were summarized and tabulated in separate categories for each endocrine involvement.

Results: Among 944 studies, 36 articles were eligible for review. Growth hormone resistance and low Insulin like growth factor-1 are prevalent in patients with liver cirrhosis with negative impact on prognosis. Thyroid dysfunction is mostly seen in the form of sick euthyroid syndrome. Osteoporosis is also prevalent in cirrhosis but the exact mechanism is not clear. Adrenal insufficiency is a prevalent clinical feature both in compensated and critically ill patients with cirrhosis with negative impact on patients’ outcomes.

Conclusion: Disorders of endocrine system is prevalent in cirrhosis. These patients should be checked and treated for these disorders to achieve a stable clinical situation and prepare for liver transplantation.

Key words: Growth hormone, liver cirrhosis, non-alcoholic fatty liver disease, osteoporosis, thyroid disease


Introduction

Cirrhosis is the common end stage of acute and chronic liver damages. Nonalcoholic steatohepatitis (NASH) is going to become the leading cause of liver cirrhosis among all populations in parallel with the global increase in diabetes, obesity and metabolic syndrome.¹ In industrialized countries chronic hepatitis C and alcoholism are still two leading causes of cirrhosis.² Autoimmune hepatitis, metabolic liver disease, Wilson disease and primary biliary cirrhosis are among other causes of liver cirrhosis.

Irrespective of etiology, liver cirrhosis and its complications can affect other body organs and cause a great morbidity and mortality. Portal hypertension is the most important consequence of liver cirrhosis and is the main cause of death among these patients. Bleeding from gastroesophageal varices, ascites, hepatic encephalopathy, coagulopathy, and spontaneous bacterial peritonitis are all complications of cirrhosis that can be potentially lethal. Hepato-renal and hepato-pulmonary syndromes are involvement of kidneys and lungs in the context of liver cirrhosis and are warnings for poor prognosis.²³

Endocrine system is a complex, sophisticated system that involves in many physiological and pathological processes and functions in human body. Liver is thoroughly involved in proteins, cytokines, and interleukins synthesis and destruction. Therefore, abnormal function of endocrine organs is expectable in patients with liver cirrhosis. An alteration in growth hormone (GH) and insulin-like growth factor-1 (IGF-1) secretion pattern has been described in chronic liver disease.⁴ According to previous studies, Liver has an important role in metabolism of thyroxin binding globulin and alterations in thyroid hormones.⁵ Adrenal insufficiency is also seen either in patients with compensated or decompensated cirrhosis.⁶ Male patients with cirrhosis have clinical features of hypogonadism like gynecomastia, loss of libido and infertility while women experience amenorrhea or oligomenorrhea.⁷ Disorders of bone metabolism and alterations in serum prolactine level have been also described.⁸

In this study, we reviewed current literature about endocrine abnormalities in patients with liver cirrhosis.

Materials and Methods

Search strategy
The study was conducted using PRISMA (Preferred reporting items for systematic review and meta-analyses) guidelines, flow diagram and checklist.⁹ A computerized English language literature search of PubMed was performed in September 2012. Studies that had been published after January 1990 were included to be reviewed. Studies on animal models were excluded. After a preliminary search in MeSH database, we categorized our search to five steps according to endocrine organ. We used terms, “liver cirrhosis” and “thyroid”, “liver cirrhosis” and “growth hormone”, “liver cirrhosis” and “insulin like growth factor-1 (IGF-1)”, “liver cirrhosis” and “adrenal insufficiency”, “liver cirrhosis” and “os-
teoporosis”, “liver cirrhosis” and “osteomalacia”, “liver cirrhosis” and “hypogonadism”, “liver cirrhosis” and “diabetes”, and “liver cirrhosis” and hypothalamus/pituitary as key words in titles and/or abstracts.

Eligibility and critical appraisal of the studies
A large number of references (study titles and abstracts) was reviewed and carefully appraised in this study. All descriptive/analytical cross sectional, and case-control studies, as well as clinical trials with proper methods for assessment of liver cirrhosis and measurement of hormones were included. Editorials, case reports, letters to the editor, hypotheses, studies on animals or cell lines, as well as abstracts from conferences or unpublished reports were excluded. Studies on patients with chronic viral hepatitis, acute liver failure, hepatocellular carcinoma, and drug-induced hepatitis were also excluded (Figure 1).

Data extraction
Two reviewers abstracted data from full-texts of all relevant articles. Data from these articles reports thyroid hormone abnormalities in cirrhosis, adrenal insufficiency in cirrhosis, as well as the prevalence of osteoporosis in cirrhosis and prognostic value of IGF-1/GH in cirrhosis were extracted and outlined in separate tables.

Results
As a result of our electronic search, 110 studies out of 944 studies were reviewed and appraised for relevance and validity. After exclusion of studies with other determinants, studies that are not representative of our aims, case reports, editorials, finally 36 studies were included and the results were categorized in sub sections. Ten studies reported GH/IGF-1 level in liver cirrhosis and their prognostic significance in these patients. These studies showed that GH resistance and low IGF-1 are prevalent in patients with liver cirrhosis with negative impact on prognosis (Table 1). Seven cross-sectional studies were found to investigate thyroid hormone abnormalities in patients with liver cirrhosis (Table 2). Nine studies reported the prevalence of osteoporosis in liver cirrhosis (Table 3). Osteoporosis was more prevalent in lumbar area and in patients with primary biliary cirrhosis as underlying cause of liver cirrhosis. There were ten studies reporting prevalence of adrenal insufficiency in patients with liver cirrhosis. Adrenal insufficiency was a prevalent clinical feature both in compensated and critically ill patients with cirrhosis with negative impact on patients’ outcomes (Table 4).
Table 1. Prognostic value of IGF-1/ GH in patients with liver cirrhosis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Underlying disease</th>
<th>Correlation with liver dysfunction</th>
<th>Pattern of abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehghani et al.18</td>
<td>45</td>
<td>Viral/metabolic/PFIC</td>
<td>+</td>
<td>IGF-1 &amp; IGFBP-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSC/Wilson/BA Cryptogenic</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Assy et al.19</td>
<td>53</td>
<td>cryptogenic / viral</td>
<td>+</td>
<td>IGF-1</td>
</tr>
<tr>
<td>Lorenzo-Zuniga et al.20</td>
<td>40</td>
<td>HCV</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Wu et al.21</td>
<td>44</td>
<td>Viral</td>
<td>+</td>
<td>IGF-1 &amp; IGFBP-3</td>
</tr>
<tr>
<td>Viyantiadis et al.22</td>
<td>40</td>
<td>Viral/PBC/alcoholic</td>
<td>+</td>
<td>IGF-1</td>
</tr>
<tr>
<td>Donaghy et al.23</td>
<td>50</td>
<td>Viral/PBC/PAH</td>
<td>+</td>
<td>IGF-1, IGFBP-3</td>
</tr>
<tr>
<td>Moller et al.23</td>
<td>38</td>
<td>NA</td>
<td>-</td>
<td>GHBP</td>
</tr>
<tr>
<td>Assy et al.24</td>
<td>15</td>
<td>NA</td>
<td>-</td>
<td>IGF-1,IGFBP-3</td>
</tr>
<tr>
<td>Caregaro et al.25</td>
<td>64</td>
<td>NA</td>
<td>+</td>
<td>IGF-1</td>
</tr>
<tr>
<td>Moller et al.26</td>
<td>36</td>
<td>Alcoholic</td>
<td>+</td>
<td>IGF-1</td>
</tr>
</tbody>
</table>

IGF-1 = insulin like growth factor-1, GH = growth hormone, IGFBP-3 = insulin like growth factor binding protein-3, GHBP = growth hormone binding protein, PFIC = progressive fibrosing intrahepatic cholestasis, BA = biliary atresia, PBC = primary biliary cirrhosis, PSC = primary sclerosing cholangitis, AIH = autoimmune hepatitis, HCV = hepatitis C virus, NA = not available.

Table 2. Thyroid hormone abnormalities in liver cirrhosis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Underlying disease</th>
<th>Prevalence of TD</th>
<th>Pattern of abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corpechot39</td>
<td>205</td>
<td>PBC</td>
<td>26 (13%)</td>
<td>AITD</td>
</tr>
<tr>
<td>Caregaro40</td>
<td>75</td>
<td>Alcoholic/viral</td>
<td>23 (30.6%)</td>
<td>T4</td>
</tr>
<tr>
<td>Moustafa41</td>
<td>59</td>
<td>HCV</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Tas42</td>
<td>106</td>
<td>Viral/AIH/PBC/Wilson/ Cryptogenic/Alcohol</td>
<td>65 (61.3%)</td>
<td>SUS</td>
</tr>
<tr>
<td>El-Kabbany36</td>
<td>40</td>
<td>Viral/Metabolic/AIH/BA/Bililiary/Wilson</td>
<td>NA</td>
<td>FT3</td>
</tr>
<tr>
<td>Seehofer48</td>
<td>22</td>
<td>Viral/PBC/Alcohol/ Cryptogenic</td>
<td>NA</td>
<td>FT3, T3</td>
</tr>
<tr>
<td>Silveira44</td>
<td>67</td>
<td>PBC</td>
<td>9 (13.4%)</td>
<td>Hypo &amp; hyperthyroidism</td>
</tr>
</tbody>
</table>

PBC = primary biliary cirrhosis, AITD = autoimmune thyroid disease, HCV = hepatitis C virus, AIH = autoimmune hepatitis, BA = biliary atresia, SUS = sick euthyroid syndrome, NA = not available.

Table 3. Prevalence of osteoporosis in patients with liver cirrhosis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Underlying disease</th>
<th>Prevalence of Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahmoudi60</td>
<td>109</td>
<td>Viral/Alcoholic</td>
<td>11% lumbar 3.6% femur</td>
</tr>
<tr>
<td>Loria 41</td>
<td>35</td>
<td>Alcoholic/viral</td>
<td>14% femur</td>
</tr>
<tr>
<td>Guanabens62</td>
<td>185</td>
<td>PBC</td>
<td>30.6% lumbar 12.9% femur</td>
</tr>
<tr>
<td>Wariaghi63</td>
<td>64</td>
<td>Viral/PBC</td>
<td>42.1% lumbar &amp; hip</td>
</tr>
<tr>
<td>Guichelaar48</td>
<td>360</td>
<td>PBC/PSC</td>
<td>37% lumbar</td>
</tr>
<tr>
<td>Sokhi65</td>
<td>104</td>
<td>Viral</td>
<td>8.6% lumbar 2.9% femur</td>
</tr>
<tr>
<td>Carey66</td>
<td>207</td>
<td>Viral/Alcoholic</td>
<td>13.8% lumbar</td>
</tr>
<tr>
<td>Ninkovic67</td>
<td>243</td>
<td>Mixed</td>
<td>36.6% lumbar &amp; femur</td>
</tr>
<tr>
<td>Monegal68</td>
<td>58</td>
<td>Mixed</td>
<td>43%</td>
</tr>
</tbody>
</table>

PBC = primary biliary cirrhosis, PSC = primary sclerosing cholangitis.
Discussion

Growth hormone (GH) and insulin like growth factor-1 (IGF-1)

Liver has a central role in GH/IGF-1 axis, since it is the major source of IGF-1. GH is produced in anterior pituitary gland and stimulates production of IGF-1 in the liver by induction of IGF-1 gene transcription in hepatocytes.10 IGF-1 has a negative feedback effect on GH production and secretion via local inhibitory action on anterior pituitary gland and inhibitory effect on somatostatin secretion from hypothalamus.19

Basal plasma GH level is increased in patients with liver cirrhosis.12 This may be in part to an increased response to GH releasing hormone in these patients.13 On the other hand, serum level of IGF-1 is low in cirrhotic patients as a result of diminished response to GH.14 Therefore, the negative inhibitory feedback effect of IGF-1 is lacked and results in substantial increase in GH level. Decreased IGF-1 level is secondary to reduced hepatocyte mass, decreased GH receptors in cirrhotic liver, and IGF binding proteins (IGFBP) as blockers of IGF-1 action.15,16 These alterations in GH/IGF-1 axis have been proposed to be responsible for disorders of lipid and carbohydrate metabolism, insulin resistance and low bone mass in patients with liver cirrhosis.17

According to Table 2, several studies have demonstrated the prognostic value of IGF-1 and GH in liver cirrhosis. Almost all of these studies reported that low IGF-1, and IGFBP-3 is associated with more severe diseases. This finding can be attributed to the development of complications of cirrhosis like malnutrition,27 insulin resistance,28 osteoporosis,29 and impaired immune function10 in low IGF-1 state.

Low serum levels of IGF-1 and IGFBP-3 have also been correlated with development of hepatocellular carcinoma (HCC) in patients with cirrhosis. In a prospective study by Mazziotti, et al., development of HCC was associated with a reduction in serum IGF-1 independent of grade of cirrhosis. They also suggested that follow up of serum IFG-1 may be useful in precocious diagnosis of tumors.31 Another study has suggested IGFBP-3 as a better predictor of HCC compared to IGF-1 in cirrhosis.32

Recently a randomized placebo controlled clinical trial showed beneficial effect of IGF-1 administration in increasing albumin level and improvement of energy metabolism in patients with cirrhosis.33 However, it should be noted that high serum levels of IGF-1 has been reported to be associated with cancer development and this point may limit the clinical utilization of IGF-1 therapy in cirrhotic patients.

Thyroid dysfunction in liver cirrhosis

Several abnormal alterations in thyroid gland have been identified in patients with liver cirrhosis. These are ranged from alterations in thyroid size, morphology and architectural pattern to alterations in thyroid hormone metabolism and regulation. From
morphological aspect, thyroid glandular volume has been reported to be increased up to 17% in patients with cirrhosis compared to non-cirrhotic controls. Thyroid volume is significantly increased in Child C cirrhosis rather than compensated cirrhosis. Resistant and pulsatility indices of inferior thyroid artery are increased in cirrhotic patients with respect to healthy individuals. Peripheral vascular fibrosis, shorter and thinner follicular diameter and epithelial width were histological features of thyroid gland in cirrhotic patients when compared to non-cirrhotic groups.

Liver is the main organ involved in the peripheral conversion of tetraiodothyronine (T4) to triiodothyronine (T3) and is the manufacturer of many proteins including thyroid binding proteins. Therefore, dysregulation and dysfunction of thyroid hormones are anticipated in patients with cirrhosis. Studies that reported thyroid hormone abnormalities were outlined in Table 1. The prevalence of thyroid hormone abnormalities ranged from 13 to 61%. A recent study reported that nearly 61% of patients with liver cirrhosis admitted in intensive care units (ICU) had some forms of sick euthyroid syndrome. Although, hypothyroidism was more frequently seen in cirrhosis, hyperthyroidism has been also reported in patients with cirrhosis. Low T3 and low free T3 were the most common pattern of thyroid hormone abnormalities in these studies. This is probably due to reduced deiodinase 1 activity and subsequent impaired hepatic conversion of T4 to T3.

Association between severity of cirrhosis, prognosis and outcomes with thyroid hormone was another topic in several studies. Caregaro, et al., reported that low T4 variants of sick euthyroid syndrome has been associated with decreased short- and long-term survival of patients with liver cirrhosis. Other studies, indicated that low serum T3 is a good index of disease severity in cirrhosis. One study demonstrated that significant increase in reverse T3 was accompanied with development of hepatocellular carcinoma in HCV cirrhosis. A retrospective study suggested that a mild controlled hypothyroidism is beneficial in cirrhosis as liver function tests tend to be better in hypothyroid state.

Bone related disorder in cirrhosis

The term hepatic osteodystrophy refers to bone disorders related to chronic liver disease and cirrhosis. The most prevalent bone disease is osteoporosis, however osteomalacia may also be seen (rarely) in cirrhosis. The pathophysiological basis of osteoporosis in cirrhosis is poorly understood but several mechanisms are proposed. Some risk factors of osteoporosis including malnutrition, hypogonadism, alcohol consumption and use of corticosteroid are seen in cirrhosis. Patients with primary biliary cirrhosis are mostly postmenopausal women that predispose to osteoporosis.

The role of IGF-1 has been proposed in bone metabolism and maintenance of bone mass. Therefore, reduced levels of IGF-1 in cirrhosis may contribute to reduced bone mass and osteoporosis. George, et al., showed that lower serum levels of IGF-1 were associated with low bone mineral density in patients with cirrhosis. Osteoprotegerin (OPG) is a member of tumor necrosis factor receptor superfamily that is secreted from osteoblasts and has an inhibitory effect on osteoclast differentiation. Recent studies in patients with cirrhosis have illustrated the protective effect of OPG not only in bone loss but also in progression of liver disease. Prevalence of osteoporosis has been reported in several studies (Table 3). In these studies osteoporosis was defined as T-score <-2.5. As reported in these studies, osteoporosis is more prevalent in lumbar spine compared to femoral neck among patients with liver cirrhosis. The prevalence of osteopenia (T-score <-1) is even higher than osteoporosis in these patients.

Figure 2. Possible mechanisms of hypogonadism in cirrhosis. IGF-1 = insulin like growth factor-1, DHT = dihydroepiandrosterone, SHBG = sex hormone binding globulin.
Adrenal insufficiency in liver cirrhosis

Adrenal insufficiency is a common feature in critically ill patients. Adrenal insufficiency has been reported both in patients with compensated and stable cirrhosis as well as in cirrhotic patients in septic shock.69 Sometimes the adrenal disorder in the context of liver disease is called hepatoadrenal syndrome,70 although the mechanisms of hypothalamus-pituitary-adrenal (HPA) axis dysfunction are not clear in liver disease. Low level of cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) are established laboratory findings in cirrhosis.71 Cholesterol is a precursor for adrenal gland to produce steroids. When cholesterol level is decreased the adrenal gland will no longer have enough substrate to produce hormones. On the other hand, tumor pro-inflammatory cytokines especially necrosis factor alpha (TNF-α), with increased level in cirrhosis, has been reported to reduce adreno-cortico-tropic-hormone (ACTH) secretion from pituitary gland.72 These features are more severe in patients with higher Child Pugh score.84 Erectile dysfunction and reduced sexual activity are seen in patients with more severe cirrhosis. The severity of cirrhosis is assessed using the model for end-stage liver disease (MELD).85

Above mentioned abnormalities are more prominent in patients with alcoholic cirrhosis due to direct effect of ethanol on testis.86 Several hormonal abnormalities are responsible for these clinical alterations. Testosterone and dihydroepiandrosterone (DHEA) levels are decreased in alcoholic cirrhosis.87 Testosterone is responsible for maintaining normal spermatogenesis.88 The high incidence of diabetes in patients with liver cirrhosis has been known from years ago.92 On the other hand, patients with diabetes are more susceptible to chronic liver disease and HCC.93 Metabolic syndrome and diabetes are not only prevalent among patients with chronic liver diseases but also can occur after liver transplantation.94–97 The terms non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are hepatic manifestations of insulin resistance and metabolic syndrome.98 In patients with NAFLD, the incidence of type II diabetes is increased independent of insulin resistance and obesity.99 Based on these findings, screening of patients with NAFLD for type II diabetes have been suggested by some authors.100

Insulin resistance (IR) is central to pathogenesis of NAFLD. Accumulation of triglycerides and steatosis as consequence of systemic IR is the first hit in “two hit hypothesis” described by Day, et al.101 Oxidative stress secondary to long term accumulation of triglycerides is the second hit in this theory. The “multiple hit hypothesis” suggests multiple parallel phenomenons are acting together in pathogenesis of NAFLD and subsequent liver fibrosis.102 Irrespective of these two main hypotheses, IR is the main underlying cause for NAFLD and NASH.

Thyroid hormone abnormalities have been shown in patients with NAFLD.103–105 We have recently shown that a pattern of sick euthyroid syndrome is prevalent in patients with NAFLD and the diagnosis of NAFLD is significantly higher in those with lower TSH.100 Our observation have been recently confirmed in an animal model of NAFLD.106

Hypogonadism is a frequent clinical feature in patients with liver cirrhosis. These patients have gynecomastia, decreased libido, signs of feminization, testicular atrophy and low testosterone level, as well as infertility and reduced spermatogenesis.83 These features are more severe in patients with higher Child Pugh score.84 Erectile dysfunction and reduced sexual activity are seen in patients with more severe cirrhosis.85 The severity of cirrhosis is assessed using the model for end-stage liver disease (MELD).85

Several hormonal abnormalities are more prominent in patients with alcoholic cirrhosis due to direct effect of ethanol on testis.86 Several hormonal abnormalities are responsible for these clinical alterations. Estrogen/androgen ratio has been increased in cirrhosis while there is a reduction in serum testosterone and dihydroepiandrosterone level.87 A mild elevation in serum estradiol has been also showed in several studies.88 Hyperprolactinemia is present in patients with cirrhosis and may involve in hypogonadism by an inhibitory effect on gonadotropin.89 Sex binding hormone globulin (SHBG), a protein which is produced by the liver and binds to testosterone with high affinity. Estrogens have a stimulatory effect on production of SHBG, while androgens inhibit its production and secretion.109 Conditions with excess estrogen accompany with increased production of SHBG and subsequent reduction in free testosterone and dihydroepiandrosterone.89 This may also participate in feminized features in cirrhosis. Finally, we should remind the role of IGF-1 in hypogonadism. IGF-1 stimulates testosterone production and spermatogenesis. Therefore, IGF-1 deficiency as seen in cirrhosis can result in hypogonadism (Figure 2). Female patients with cirrhosis suffer from amenorrhea, oligomenorrhea, or irregular episodes of metrorrhagia.85 These alterations are generally normalized after liver transplantation.

Metabolic syndrome and insulin resistance in liver disease

Metabolic syndrome is a constellation of metabolic abnormalities including diabetes, hyperlipidemia, central obesity and hypertension.89 The high incidence of diabetes in patients with liver cirrhosis is approximately 20% to 50%.108

Hyperinsulinemia, hypertriglyceridemia, increased plasma levels of free fatty acids, and reduced lipoprotein lipase activity are seen in patients with liver cirrhosis. These features are usually between 20% to 50%.108 Accumulation of triglycerides is the second hit in this theory. The “multiple hit hypothesis” suggests multiple parallel phenomenons are acting together in pathogenesis of NAFLD and subsequent liver fibrosis.102 Irrespective of these two main hypotheses, IR is the main underlying cause for NAFLD and NASH.

Here in, we reviewed available evidences about endocrine system abnormalities in patients with liver cirrhosis. Endocrine hormones are proteins and steroids that are produced and secreted by different endocrine glands. Liver is an organ, which is totally involved in metabolism and catabolism of many hormones in the body and has a close interaction with endocrine system. Growth hormone resistance with low serum IGF-1 is prevalent in liver cirrhosis that may result in insulin resistance, osteoporosis and hypogonadism. Liver cirrhosis can affect thyroid mainly in forms of sick euthyroid syndrome or hypothyroidism, although most of the patients are clinically euthyroid. Adrenal insufficiency, osteoporosis and hypogonadism are other clinical abnormalities of endocrine system in liver cirrhosis.
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None.

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کارگاه‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

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