Original Article
The predictive value of microRNA in early hypertensive disorder complicating pregnancy (HDCP)

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Abstract: Objective: To examine the predictive value of microRNA (miRNA) in hypertensive disorder complicating pregnancy (HDCP). Methods: 102 pregnant women with HDCP admitted to our hospital from March 2017 to June 2019 were recruited as the study cohort and randomly divided into an HDCP group, a mild preeclampsia group, and a severe preeclampsia group, with 34 patients in each group. In addition, 34 healthy pregnant women who underwent pregnancy tests in our hospital were recruited as the normal group. The relative expressions of plasma miR-19a, miR-126, and miRNA-210 in were measured. A Pearson correlation analysis was used to analyze the correlations between the miR-19a, miR-181b, and miRNA-210 expressions and the severity of HDCP. Receiver operating characteristic (ROC) curves were used to evaluate the diagnostic efficacy of the miR-19a, miR-126, and miRNA-210 expressions. Results: The miR-19a and miRNA-210 expressions were higher in the HDCP group, the mild preeclampsia group, and the severe preeclampsia group than they were in the normal group, and the miR-126 expression was lower (all P<0.05). The miR-19a, miR-126, and miRNA-210 expressions were different among the four groups (P<0.05). The miR-19a and miRNA-210 expression levels in the severe preeclampsia group were higher than they were in the HDCP group, and the miR-126 expression was lower (P<0.05). A Pearson correlation analysis showed the miR-19a and miR-210 levels in the HDCP patients were positively correlated with the severity of the disease (P<0.05), and the miR-126 level is negatively correlated with disease severity (P<0.05). Our ROC curve analysis demonstrated that the miR-19a and miR-210 levels in the HDCP patients were positively correlated with the severity of the disease (P<0.05), and the miR-126 level is negatively correlated with disease severity (P<0.05). Our ROC curve analysis demonstrated that the miR-19a, miR-126, and miR-210 levels have a predictive value for HDCP. The areas under the curve were 0.800, 0.633, and 0.723 , the sensitivities were 81.2%, 71.4%, and 80.2% , and the specificities were 73.5%, 67.5%, 81.5%. Additionally, the area under the curve of the combination of the three was 0.896, and the sensitivity and specificity were 90.5% and 93.9% respectively. Conclusion: miR-19a, miR-126, and miR-210 are strongly connected to the severity of HDCP and can be used as a sensitive indicator to predict HDCP patients clinically.

Keywords: MicroRNA, hypertension during pregnancy, pre-eclampsia

Introduction
Hypertensive disorder complicating pregnancy (HDCP) is a series of diseases with pregnancy and high blood pressure involved, and is one of the leading causes of illness and death among mothers and babies [1]. The primary clinical manifestations of the diseases include elevated blood pressure, edema, and systematic multiple organ damage. In severe cases, coma and convulsions may even occur, and they have a negative impact on the health of mothers and babies [2]. According to reports [3], the incidence rate of this disease in China is 9.4%, and it is approximately 7%-12% abroad. The pathogenesis of HDCP remains obscure, so an early diagnosis and assessment of the severity of the disease is therefore a vital way to implement effective treatment to delay the progression of HDCP. Multiple recent studies have found that [4] miRNAs are involved in regulating apoptosis, proliferation, cell differentiation, organ formation, and the aging of organisms and are closely associated with the occurrence of diseases such as inflammation, diabetes, malignant tumors, and hypertension. Previous studies reported [5, 6] that, among a variety of microRNAs, miR-19a, miRNA-210, and miR-126 are highly expressed in placental tissue and the peripheral blood of pregnant women with preeclampsia and are strongly connected to preeclampsia. The disease’s occurrence and development are closely related. Nevertheless, there is paucity of evidence regarding microR-
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Table 1. Comparison of the baseline data between the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Case group (n=102)</th>
<th>Control group (n=34)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.26±5.12</td>
<td>27.30±5.10</td>
<td>0.039</td>
<td>0.969</td>
</tr>
<tr>
<td>gestational weeks</td>
<td>29.40±6.48</td>
<td>28.77±6.45</td>
<td>0.492</td>
<td>0.624</td>
</tr>
<tr>
<td>Gravidity (times)</td>
<td>1.26±0.26</td>
<td>1.30±0.24</td>
<td>0.791</td>
<td>0.430</td>
</tr>
<tr>
<td>BIM (Kg/m²)</td>
<td>23.14±3.12</td>
<td>23.26±3.17</td>
<td>0.194</td>
<td>0.847</td>
</tr>
</tbody>
</table>

Methods

Subjects

This study was a controlled analysis conducted on 102 pregnant women with HDCP admitted to our hospital from March 2017 to June 2019, and these participants were assigned into the case groups. Additionally, 34 healthy pregnant women who underwent pregnancy screening in our hospital during the same period were placed in the normal group. The P-value for the general comparison was greater than 0.05, and this suggested the fitness of the participants (Table 1). According to the HDCP diagnosis and classification criteria, the case group patients were classified into 34 patients in the HDCP group, 34 patients in the mild pre eclampsia group, and 34 patients in the severe pre eclampsia group. This study was registered and approved by the medical ethics committee of our hospital, and the patients and their families involved in the study participated voluntarily.

Inclusion criteria: (1) Patients who met the diagnostic criteria for hypertension during pregnancy [7]. (2) Patients with a gestational age ≥20 weeks. (3) Patients with a systolic blood pressure ≥140 mmHg (1 mmHg=0.133 kPa) and a diastolic blood pressure ≥90 mmHg and whose blood pressure returned to normal within 12 weeks after delivery and whose urine protein tested negative. Exclusion criteria: (1) Patients who used immunosuppressants and glucocorticoid hormones for a long time. (2) Patients suffering from mental illnesses, cancer, or systemic inflammation diseases. (3) Patients with coagulation dysfunction. (4) Patients with cardiopulmonary insufficiency.

Statistical methods

This study was carried out using the SPSS 22.0 statistical package. [n (%)] and x ± s were calculated for the qualitative data and quantitative data, respectively, and chi-square and t-tests were respectively used to determine whether the results differed statistically. Correlation was analyzed using Pearson correlation analyses, and ROC curves were calculated to evaluate the diagnostic value of miR-19a, miR-126, and miRNA-210. Significance in the current study was claimed at a P-value of <0.05.

Results

The serum miR-19a, miR-126, and miRNA-210 expression levels

The serum miR-19a and miRNA-210 levels were found to be higher in the case group as compared with the control group; in contrast, the miR-126 level was shown to be lower when compared with the control group, and the difference between the two groups was significant (P<0.05, Table 2).
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The serum miR-19a, miR-126, and miRNA-210 expression levels in the two groups of patients

Table 2.

<table>
<thead>
<tr>
<th>Group</th>
<th>miR-19a</th>
<th>miR-126</th>
<th>miRNA-210</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case group (n=102)</td>
<td>9.65±3.78</td>
<td>1.98±0.66</td>
<td>6.77±2.43</td>
</tr>
<tr>
<td>Control group (n=34)</td>
<td>2.02±0.78</td>
<td>8.95±3.54</td>
<td>1.50±0.54</td>
</tr>
<tr>
<td>t</td>
<td>11.530</td>
<td>11.290</td>
<td>12.340</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The differences in the serum miR-19a, miR-126, and miRNA-210 levels in the HDCP patients with different degrees of disease were statistically significant (P<0.05). Higher miR-19a and miRNA-210 expressions were identified in the severe preeclampsia group compared with the HDCP group, and the miR-126 expressions were found to be lower when compared with the HDCP group (P<0.05). See Table 3.

The correlation between the miR-19a, miR-181b, and miRNA-210 expression levels in each HDCP subgroup

Table 3.

<table>
<thead>
<tr>
<th>Group</th>
<th>miR-19a</th>
<th>miR-126</th>
<th>miRNA-210</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDCP group (n=34)</td>
<td>6.60±3.78</td>
<td>15.65±5.23</td>
<td>3.37±1.41</td>
</tr>
<tr>
<td>mild preeclampsia group (n=34)</td>
<td>11.64±3.80*</td>
<td>9.38±2.57*</td>
<td>6.63±2.04*</td>
</tr>
<tr>
<td>severe preeclampsia group (n=34)</td>
<td>17.88±5.72**</td>
<td>5.95±2.56**</td>
<td>10.65±4.33**</td>
</tr>
<tr>
<td>t</td>
<td>5.483</td>
<td>2.873</td>
<td>1.678</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.098</td>
</tr>
</tbody>
</table>

Note: *means compared with the HDCP group, P<0.05; **means compared with the mild preeclampsia group, (P<0.05).

The correlation between the miR-19a, miR-181b, and miRNA-210 expression levels in the plasma of the HDCP pregnant women and the severity of the disease

Table 4.

<table>
<thead>
<tr>
<th>Item</th>
<th>miR-19a</th>
<th>miR-126</th>
<th>miRNA-210</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of the disease</td>
<td>0.336</td>
<td>-0.146</td>
<td>0.0256</td>
</tr>
<tr>
<td>r</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>0.014</td>
</tr>
</tbody>
</table>

The serum miR-19a, miR-181b, and miRNA-210 expression levels in the patients with different degrees of HDCP

The differences in the serum miR-19a, miR-126, and miRNA-210 levels in the HDCP patients with different degrees of disease were statistically significant (P<0.05). Higher miR-19a and miRNA-210 expressions were identified in the severe preeclampsia group compared with the HDCP group, and the miR-126 expressions were found to be lower when compared with the HDCP group (P<0.05). See Table 3.

The correlation between the miR-19a, miR-181b, and miRNA-210 expressions in the plasma of the pregnant women with HDCP and the disease severity

Our Pearson correlation analysis showed that the serum miR-19a and miR-210 expressions in the HDCP patients were positively correlated with the severity of the disease (P<0.05) and miR-126 was negatively associated with the severity of the disease (P<0.05), as presented in Table 4.

The diagnostic value of serum miR-19a, miR-126, miR-210 in HDCP

The findings of our ROC curve analysis demonstrated that the serum miR-19a, miR-126, and miR-210 expressions have a certain predictive value for HDCP. The areas under the curve were 0.800, 0.633, and 0.723, the sensitivities were 81.2%, 71.4%, and 80.2%, and the specificities were 73.5%, 67.5%, and 81.5%. Additionally, the area under the curve of the combination of the three was 0.896, and the sensitivity and specificity were 90.5% and 93.9%. The comparison of the areas under the curve between the three indicators was insignificant (P>0.05), see Table 5 and Figure 1.

Discussion

MicroRNA is a nucleic acid substance composed of about 80 single-stranded small molecules [8]. Previous studies have shown [9, 10] that up to 1/3 of human genes are potential target genes of microRNAs, which can inhibit target gene expression by binding to target gene transductions and participating in the occurrence and regulation of diseases. There are many types of miRNA, and most of them have the sequential and phase characteristics of differentiation, but the biological functions of the different types are also very discernable, so they have a greater impact on gene expression, and even play direct regulatory roles [11]. According to earlier studies [12], MiRNA can be viewed as a biomarker of hypertension and has a high diagnostic value. Accordingly, numerous trials have screened various types of microR-
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Table 5. The diagnostic value of the serum miR-19a, miR-126, and miR-210 expression levels in HDCP

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Cut-off value</th>
<th>AUC</th>
<th>95% CI</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-19a</td>
<td>9.435</td>
<td>0.800</td>
<td>0.721~0.945</td>
<td>81.2%</td>
<td>73.5%</td>
</tr>
<tr>
<td>miR-126</td>
<td>8.642</td>
<td>0.633</td>
<td>0.601~0.705</td>
<td>77.4%</td>
<td>87.5%</td>
</tr>
<tr>
<td>miR-210</td>
<td>5.150</td>
<td>0.723</td>
<td>0.638~0.876</td>
<td>80.2%</td>
<td>81.5%</td>
</tr>
<tr>
<td>Combined</td>
<td>-</td>
<td>0.896</td>
<td>0.802~0.945</td>
<td>90.5%</td>
<td>93.9%</td>
</tr>
</tbody>
</table>

An early clinical diagnosis and timely effective treatment and preventive measures for HDCP are particularly important for improving pregnancy outcomes because HDCP causes many complications. Therefore, for HDCP, the determination of peripheral plasma biomarkers is of great significance. To further clarify the relationship between the expressions of miR-19a, miR-126, miR-210, and HDCP, the authors divided the case group into an HDCP group, a
mild preeclampsia group, and a severe pre-
eclampsia group according to the severity of
HDCP, aiming to explore the changes in the
miR-19a, miR-126, and miR-210 expression
levels. We found that the miR-19a and miR-210
expression levels showed an upward trend
along with the severity of the disease, indicat-
ing that the miR-19a and miR-210 expression
levels were significantly increased in all stages
of HDCP, and it was vice versa with miR-126.
Previous studies found that [20] in the early
stage of HDCP, the miR-19a expression can rise
to more than 2 times its normal level, and the
increase can be as high as 4 fold in severe pre-
eclampsia. Some studies found that [21] that
the down-regulation of specific microRNA-126
expressions will reduce angiogenesis and hy-
poxia in the right ventricle. Furthermore, a
Pearson correlation analysis indicated that the
serum miR-19a and miR-210 expression levels
in HDCP patients were positively correlated
with disease severity, and the miR-126 expres-
sion level was negatively correlated. Import-
antly, our ROC curve analysis showed that the
area under the curve of the three combined
was 0.896, and the sensitivity and specificity
were 90.5% and 93.9%. Moreover, no statisti-
cally significant differences were observed in
the areas under the curve between the three
indicators. Taken together, these indicators
have a higher specificity and sensitivity in
HDCP. This highlights that there is a need to
carry out early intervention measures based on
the clinical diagnosis for these patients to
reduce the incidence of HDCP. The potential
mechanism is that the low expression of plas-
ma miR-126 may be involved in the abnormal
recasting of the uterine spiral artery, leading to
an insufficient blood supply at the maternal-
fetal interface, a reduction of effective placen-
tal perfusion, local tissue ischemia, hypoxia,
and abnormal placental structure, which ulti-
mately leads to vascular inflammation reac-
tions and endothelial cell dysfunction. Addi-
tionally, miR-210 is a hypoxic activating factor.
When the body is ischemic and hypoxic, the
expression of miR-210 in tissues is up-regulat-
ed and promotes the formation of new blood
vessels. A high expression of miR-210 in preg-
nant women can cause abnormal trophoblast
cells, leading to an insufficient blood supply to
the placenta [22]. Our study has several limita-
tions due to the fact that it was hospital-based,
with a small cohort. This needs to be addressed
by expanding the cohort and conducting a mul-
ticenter, prospective study with a long-term
follow-up.

In summary, miR-19a, miR-126, and miR-210
are strongly connected to disease severity in
HDCP patients, and they can be used as sensi-
tive indicators for predicting HDCP.

Disclosure of conflict of interest

None.

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